Biochimie 200 (2022) 44–59

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Oncostatic activities of melatonin: Roles in cell cycle, apoptosis, and autophagy

Niloufar Targhazeh [a], Russel J. Reiter [b], Mahdi Rahimi [c, d], Durdi Qujeq [e, f], Tooba Yousefi [g], Mohammad Hassan Shahavi [h], Seyed Mostafa Mir [i, j, *]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Cell Systems and Anatomy, University of Texas Health Science Center, San Antonio, TX, USA
[c] Lodz University of Technology, Institute of Polymer and Dye Technology, Stefanowskiego 16, 90-537, Lodz, Poland
[d] International Center for Research on Innovative Biobased Materials (ICRI-BioM)—International Research Agenda, Lodz University of Technology, Lodz, Poland
[e] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[f] Department of Clinical Biochemistry, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[g] Department of Clinical Biochemistry, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Iran
[h] Department of Nanotechnology, Faculty of Engineering Modern Technologies, Amol University of Special Modern Technologies, Amol, Iran
[i] Metabolic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran
[j] Department of Clinical Biochemistry, Faculty of Medicine, Golestan University of Medical Sciences, Babol, Iran

ARTICLE INFO

Article history:
Received 14 February 2022
Received in revised form
14 May 2022
Accepted 17 May 2022
Available online 23 May 2022

Keywords:
Melatonin
Anti-cancer
Cell cycle
Apoptosis
Autophagy

ABSTRACT

Melatonin, the major secretory product of the pineal gland, not only regulates circadian rhythms, mood, and sleep but also has actions in neoplastic processes which are being intensively investigated. Melatonin is a promising molecule which considered a differentiating agent in some cancer cells at both physiological and pharmacological concentrations. It can also reduce invasive and metastatic status through receptors MT1 and MT2 cytosolic binding sites, including calmodulin and quinone reductase II enzyme, and nuclear receptors related to orphan members of the superfamily RZR/ROR. Melatonin exerts oncostatic functions in numerous human malignancies. An increasing number of studies report that melatonin reduces the invasiveness of several human cancers such as prostate cancer, breast cancer, liver cancer, oral cancer, lung cancer, ovarian cancer, etc. Moreover, melatonin's oncostatic activities are exerted through different biological processes including antiproliferative actions, stimulation of anticancer immunity, modulation of the cell cycle, apoptosis, autophagy, the modulation of oncogene expression, and via antiangiogenic effects. This review focuses on the oncostatic activities of melatonin that targeted cell cycle control, with special attention to its modulatory effects on the key regulators of the cell cycle, apoptosis, and telomerase activity.

Contents

* Corresponding author. Metabolic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, I.R. Iran.
E-mail address: mostafamir1987@gmail.com (S.M. Mir).

https://doi.org/10.1016/j.biochi.2022.05.008
0300-9084/

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine), a hormone made by tryptophan metabolism, is produced in the pineal gland and many other organs [1]. This molecule has a crucial performance in the regulation of circadian rhythms, mood, sleep, etc. [2]. The synthetic procedure via tryptophan metabolism is controlled by enzymes including arylalkylamine nacetyltransferase (AA-NAT) and hydroxyindol-O-methylteransferase (HIOMT). After the synthesis of melatonin in the pineal gland, it is released into the blood and cerebrospinal fluid. Afterward, it exerts the regulatory actions throughout the organism in response to seasonal patterns and circadian rhythms [3,4] with maximal secretion occurring at night. The pineal melatonin rhythm has an important role in modulations circadian rhythms, which are regulated by the hypothalamic suprachiasmatic nucleus (SCN) [3]. The environmental light-dark cycle plays a critical role in the synchronization of the SCN; the retinas, the intrinsically photoreceptive retina ganglion cell (ipRGC), contain the photopigment, melanopsin, which response most intensely to blue light, which connected to the SCN via the retinohypothalamic tract central and peripheral sympathetic fibers connect the SCN to the pineal gland where the melatonin biosynthesis regulates by releasing of norepinephrine (NE). The following activation of the pineal β-adrenergic receptors by NE, 3′,5′-cyclic adenosine monophosphate (cAMP) level increases, which induces the biosynthesis and release of melatonin [5]. The physiological function of melatonin goes beyond circadian rhythms and sleep. Interest in this indole has increased because it is related to a variety of physiological and pathophysiological processes. The process involved includes its antioxidant function, immune modulation, and its oncostatic activity [6–9]. The possible relationship between melatonin metabolism and neoplastic processes has been intensively investigated. Melatonin exerts oncostatic functions in numerous human malignancies including those of the breast, the ovaries, the prostate, the skin, liver, etc. [10,11]. The anticancer functions of melatonin have been examined at many different levels. Disruption of melatonin's circadian rhythm by performing regular night shift work enhances the risk of certain malignancies. Melatonin exerts oncostatic effects on tumors from a broad range of origins in experimental models by suppressing tumor cell proliferation. These data accentuate the significance of endogenous melatonin as an anticancer agent. New anticancer function of melatonin involves multiple mechanisms: direct pro-apoptotic actions, antioxidant actions, decreasing the uptake of growth factors involved in tumor growth signaling pathways, increasing immunosurveillance, and anti-angiogenic effects [12]. Recently, a great deal of investigations has addressed the effects of melatonin on the cell cycle and key components of the cell cycle. It has been postulated that another mechanism concerning the anticancer effects of melatonin includes the suppression of the cell cycle as well as the suppression of cell cycle activators. This review focuses on the oncostatic activities of melatonin through cell cycle control with special attention to its modulatory effects on the key regulators of the cell cycle, apoptosis, and telomerase activity.

2. Melatonin receptors

The melatonin's complex effects in regulating several numbers of physiological processes are in part, related to receptors including those in the membrane (MT1 known as Mel1a and MT2 known as Mel1b), cytosolic binding sites, such as calmodulin and quinone reductase II enzyme (which was previously called MT3), and nuclear binding corresponding to orphan members of the superfamily RZR/ROR [13]. These receptors are coupled directly or indirectly with multiple and different signal transductions cascades and, therefore, lead to inhibitory cancer cell responses. The types of melatonin receptors, their mechanisms, and their cellular effects are summarized in Table 1. In addition to the receptor-mediated process by which melatonin reduces cancer cell growth and metastases, it also has receptor-independent actions which likely interfere with cancer cell proliferation and migration [14].

3. Mechanisms of the anticancer effects of melatonin

The oncostatic effects of melatonin have been thoroughly investigated for some cancer types but much less so for other tumors [8,15–18]. The potential mechanisms by which melatonin negatively impacts cancer cells have been widely discussed. Owing to a broad range of actions of melatonin, these mechanisms are also varied.

3.1. Regulation of estrogen metabolism

The anticancer functions of melatonin are apparent in hormone-dependent tumors and are well-known in malignancies of the prostate or the ovaries and, especially in mammary glands [19,20]. The anti-estrogenic function of melatonin is involved in its oncostatic actions in hormone-dependent mammary cancer. Owing to its capability of interacting with the estrogen receptor, melatonin is now known as a selective estrogen receptor modulator (SERM) [21].

Table 1
Types of melatonin receptors, their mechanisms, and their cellular effects.

Melatonin receptors	Tissue distribution		Coupled-G protein	Effectors	Melatonin insensitiveness	Affinity to melatonin	Physiological responses	Ref
MT1	Brain	Cerebellum, hippocampus, substantial nigra, ventral tegmental area, nucleus acumens, caudate-putamen, SCN, meninges, pituitary, Pars Tuberalis	Giα2 Giα3 Gαq Gαs	↓ AC ↑ PI ↑ Ca2+ ↑ AA	Long-term exposure of MT1 led to melatonin insensitive	Higher	Inhibition of neuronal firing	[172,173]
	Cardiovascular system	blood vessels, aorta, and heart	Gαz Gα16	↑↓ MEK/ERK			Cardiac vessels constriction	
	Kidney	Nephrons, proximal tubules	Gβγ	↓ cGMP				
	Other tissues	Immune system, testes, ovary, skin, liver, adrenal cortex, placenta, breast, retina, pancreas spleen, retina, lymphocytes						
MT2	Brain	Cerebellum, SCN	G1	↓ AC	Long-term exposure of MT2 led to melatonin insensitive	Lower	The phase shift of circadian rhythm	[174]
	Cardiovascular system	Blood vessels	G4	↑ PI ↓ cGMP			Inhibition of cardiac vessels constriction	
	Kidney	Nephrons					Inhibition of dopamine release	
	Other tissues	Lung, granulosa cells, immune cells, duodenum, adipocytes, melanocytes, eccrine sweat glands.						
MT3	Liver, kidneys, heart, adipose tissue, brain, retina, melanocytes, keratinocytes, fibroblasts.		Quinone reductase 2 (QR2), belongs to a group of reductases	↑ PI	Altered melatonin levels are related to the changes in the activity of QR_2	N/A	Detoxification Enzyme regulation	[173,175]
RZR/ROR	RZRα, RORα, RORα2, and RZRβ bind to melatonin		Nuclear receptors	N/A	N/A	N/A	Immune modulation Antioxidant enzyme regulation	[176,177]
	RZRβ	Neuronal tissues, retina						
	RZRα	Adipose tissue, the liver, human blood leukocytes, testes and cartilage						
	RZR/RORα.	Thymus and spleen of mice, hair follicles, epidermal melanocytes, epidermal keratinocytes, dermal fibroblasts and melanomas						

SNC, suprachiasmatic nucleus of the hypothalamus; AC, adenylyl cyclase; PI, phosphoinositide hydrolysis; AA, arachidonic acid.

The anti-estrogenic potential of melatonin is associated with its ability to reduce estrogen receptor (ER)-α expression, and more importantly, to block the binding of the estrogen-ER complex to the estrogen response element (ERE) on DNA [22]. Given that melatonin signaling through its receptors results in cAMP reduction and also as decreased intracellular level of cAMP is an activation signal for ERα, it is suggested that a reduction in melatonin-induced cAMP concentration is one of the mechanisms by which melatonin causes a drop in the estrogen-induced ERα transcriptional activity [23]. Another possible mechanism is melatonin's ability to bind to calmodulin (CaM) with the inactivation of the Ca2+/CaM complex [24]. CaM also facilitates the E2−ER complex binding to the ERE. Hence, the inactivation of CaM signaling by melatonin interacts with the estrogen-signaling pathway [24]. In addition, melatonin inhibits the expression and the activity of three important enzymes that contribute to estrogen synthesis and transformation, including estrogen sulfatase, P450 aromatase, and 17β-HSD type 1 [25]. Melatonin has capability to stimulate the expression of estrogen sulfotransferase, the enzyme responsible for the inactivation of the estrogen [26]. In this context, melatonin behaves as a selective estrogen enzyme modulator (SEEM) [25]. Clearly, melatonin is the unique agent which shares both SERM and SEEM properties.

3.2. Inhibition of telomerase activity

Activation of telomerase, a specialized ribonucleoprotein DNA polymerase, is a major factor in carcinogenesis in most human cancers [27]. Telomeres are nucleoprotein segments on the terminals of linear eukaryotic chromosomes. The telomeres are shortened with each cell division, making the chromosome vulnerable to damage [28]. In most progressive cancers, telomerase expression is upregulated to maintain telomere lengths; hence, the cancer cells are protected from death [28]. Melatonin inhibits telomerase activity in cancer cells in vivo; melatonin also reduces the expression of telomerase reverse transcriptase (TERT) in the mRNA subunit. This subunit is essential for the activity of telomerase and serves as an indicator of telomerase activation [27,29]. Also, the inhibitory effects of melatonin on telomerase activity are stimulated by both endogenous estrogens)17β-estradiol) and exogenous agents with estrogenic activity in estrogen-dependent tumors [30]. For example, the metallosterogen, cadmium, stimulates telomerase activity in cancer cells.

3.3. Pro-oxidant properties

One of the most significant features of melatonin related to its oncostatic function is its ability to scavenge free radicals as well as stimulate potent antioxidative enzymes, such as glutathione peroxidase, reductase, superoxide dismutase, and catalase, and the reduction of pro-oxidants [31]. In several recent research, this feature has been widely proved the carcinogenesis which induced by agents causing oxidative damage, in consequence, melatonin exerts protective effects [32,33]. Melatonin could effectively detoxify various reactive oxygen and nitrogen species, including the superoxide anion radical, hydroxyl radical, peroxynitrite anion, hydrogen peroxide, and nitric oxide [6]. Owing to this feature, melatonin has been variously used as an adjuvant in the chemo and radiotherapy treatments of cancer.

3.4. Inhibition of angiogenesis

Angiogenesis is one of the central players in the development and progression, and, more importantly, metastatic cancer [34]. Therefore, the suppression of this process is considered an important cancer treatment strategy [34]. Melatonin has direct and indirect anti-angiogenic functions [35–40]. Its direct anti-angiogenic functions are related to its inhibitory actions on the vascular-endothelial growth factor (VEGF) and endothelin-1 (ET-1) [35,39,41,42]. Melatonin also exerts indirect anti-angiogenic effects by suppressing some tumor growth factors; such as EGF and IGF, with strong mitogenic and angiogenesis stimulatory functions and also scavenging free radicals that stabilize the hypoxia-inducible factor HIF-1α [40,43,44].

3.5. Inhibition of metastasis

Melatonin reduces the invasiveness of human cancers including breast cancer [45–48], prostate cancer [49], liver cancer [43,50], oral cancer [51], lung cancer [52], ovarian cancer [53], etc. [54,55]. The anti-metastatic effects of melatonin are achieved by an increase in the expression of cell surface adhesion molecules E-cadherin, β1-integrin, and occludin, the downregulation of integrin molecules, reduction in the expression or activity of the matrix metalloproteinase, inhibition of the cytoskeleton rearrangement, induction of epithelial to mesenchymal transition, and angiogenesis suppression [54]. More importantly, overexpression of the MT1 receptor can cause an increase in the anti-invasive response of cancer cells to melatonin. It is suppressed by luzindole (an MT1/MT2 receptor antagonist), hence indicating that these effects are related to the binding of melatonin to its receptors [5].

3.6. Enhance in immune response

In addition to the pineal gland, other organs such as bone marrow, thymus, and lymphocytes, all of which are involved in the modulation of the immune response, are also potential sources for melatonin [56]. Interestingly, in contrast to endogenous melatonin, which inhibits cellular and humoral immunity, exogenous melatonin strongly induces the production of monocytes, natural killer cells, and leukocytes as well as the synthesis and the release of cytokines, including interleukin (IL)-2, IL-6, IL-12, and interferon-γ, and the tumor necrosis factor-α (TNFα) [57]. Since activation of the immune system is another means to explain the anti-tumor response to melatonin. Thus, melatonin, as an immune-enhancing agent, can be a good candidate as a therapeutic strategy for inhibiting cancer [58].

3.7. Epigenetic regulation

The term epigenetic is related to the study of heritable alterations in the gene expression that happen due to the lack of changes in the genome sequence [59]. These include the covalent modification of bases in the DNA [60]. Several important groups of enzymes that cause epigenetic changes in the levels of DNA and histones are DNA methyltransferases (DNMTs) and histone modification enzymes (histone deacetylases and histone methyltransferases([60,61]. Epigenetic changes are now accepted as additional mechanisms that modulate cell proliferation as a critical part of the neoplastic process [62,63]. Melatonin remarkably enhances the mRNA expression of several HDAC isoforms, including HDAC3, HDAC5, and HDAC7. Melatonin also increases histone H3 acetylation in the C17.2 neural stem cells, histone H3 and H4 acetylation in mice, and human SH-SY5Y neuroblastoma cells [64,65]. Long-term treatment with melatonin stimulates histone hyperacetylation in rat the brain, therefore, suggesting a role in the epigenetic regulation for this agent [66]. The increased HADC mRNA levels likely demonstrate a compensatory feedback mechanism following melatonin-stimulated histone hyperacetylation [64]. Indeed, melatonin plays a substantial role in the modulation of histone acetylation-deacetylation. The members of retinoid Z receptor (RZR)/retinoid acid receptor-linked orphan receptor (ROR), a subclass of nuclear receptors, are correlated with Melatonin [67,68]. It can be assumed that the epigenetic effects of melatonin are exerted through interaction with RORs, which act in the formation of chromatin remodeling complexes with histone acetylase activity [69]. Protein kinase C, activated by the MT1 receptor or via a direct effect of melatonin, leads to mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) activation and, consequently, histone acetylation [64,70,71]. In addition, melatonin can induce histone acetylation by phosphorylation/activation of histone acetyltransferases, such as p300 following the phosphorylation/activation of the PI3/Akt pathway [72,73].

4. Melatonin in the regulation of the cell cycle

4.1. Induction of cell cycle delay and arrest

The possible relationships between melatonin metabolism and neoplastic processes have been intensively investigated. The underlying mechanism by which melatonin suppresses tumor growth is not completely understood. Therefore, many researchers have taken a particular interest in the evaluation of the involvement of melatonin in the tumor cell cycle control as well as the regulation of the important cell cycle-related proteins. Cos et al. [74] showed that melatonin's antiproliferative effect in breast cancer was exerted on the G1 phase of the cell cycle, which makes a transition delay in the S phase. The melatonin (10^{-9} M) treatment of MCF-7 breast cancer cell lines resulted in G1/S cell cycle arrest. In this study, the authors proved that melatonin increased the duration of the cell cycle of MCF-7 cells in a significant manner [75]. This observation supports the notion that melatonin exerts its antitumor effect at least in part, through a cell-cycle-specific mechanism by delaying the entry of MCF-7 cells into mitosis [75]. In human melanoma SK-MEL-1 cells, melatonin caused cell cycle arrest in the G1 phase [76]. By investigating the exact mechanism of the melatonin oncostatic function in melanoma, the general G-coupled receptor inhibitor and pertussis toxin revealed that these antagonisms could not prevent melatonin-induced cell growth arrest, suggesting a mechanism independent of G-coupled membrane receptors [76]. The p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway has a crucial function and role in cell growth inhibition by melatonin [76]. Liu et al. demonstrated that melatonin delayed cell proliferation by inducing G1 and G2/M phase arrest in the human osteoblastic cell line hFOB 1.19 [77] and these inhibitory effects are mediated by the ERK signaling pathway [78]. Marelli et al. [79] examined the growth-inhibitory activity of melatonin on human androgen-independent DU 145 prostate cancer cells. They reported that melatonin at physiological doses significantly suppressed DU 145-cell proliferation through the induction of cell cycle interruption by causing the accumulation of cells in the G0/G1 phase. Similar results were demonstrated for the prostate cancer LNCaP cell lines. Moretti et al. [80] showed that melatonin at nanomolar concentrations significantly inhibited the proliferation of LNCaP cells. Moreover, it affected cell cycle distribution to induce an accumulation of cells in G0/G1 and a reduction of cell number in the S phase. Thus, melatonin exerted direct antiproliferative action on androgen-dependent prostate cancer cells. Membrane receptors were not involved in the oncostatic action of melatonin in either cell line [79,80]. In contrast to these studies, the inhibitory effects of

melatonin on the proliferation of the human choriocarcinoma JAr cells as well as the proliferation and induction of GI/S cell cycle transition were reported to be MT2 melatonin receptor-dependent; the selective MT2 melatonin receptor ligand and 4-phenyl-2-propionamidotetraline (4-P-PDOT) were found to not only exert concentration-dependent anti-proliferative actions on cancer cells but also additive effects by melatonin in inhibiting JAr cell proliferation [81]. In hepatocarcinoma cell lines such as Bel7402 and SMMC-7721, melatonin treatment resulted in cell cycle arrest in the G0/G1 phase through the downregulation of p-AKT and c-myc [82]. However, in the hepatocarcinoma HepG2 cell line, melatonin induced cell cycle arrest in the G2/M phase via the upregulation of JNK 1,-2, -3, and p38, members of the MAPK family [83]. In addition, in the B65 rat dopaminergic neuroblastoma cells, melatonin increased the percentage of cells in the G1-phase of the cell cycle [84]. Several reports also indicated that melatonin may not act as a crucial role in the growth of cancer cells, including those of PC3 prostate cancer cells [85], K562 human leukemia cell line [86], A549 lung cancer cells [87], HeLa cervical cancer cells [88], MG-63 osteosarcoma cell line [88], and TK6 lymphoblastoid cell lines [88]. An explanation for these seemingly divergent findings has not been provided.

4.2. Suppression of cyclin-dependent kinases

Strongly coordinated and organized collaboration between cyclin-dependent kinases (CDK), CDK inhibitors (CDI), and cyclins are necessary for the progression through the cell cycle phases (G0/G1, S, G2, and M) [89]. The CDK family includes serine/threonine kinases with a specific catalytic core and more than 21 members identified [90]. Based on the sequence of the kinase domain, CDKs belong to the CMGC group of kinases (named after the initials of certain members such as CDK-like kinases, glycogen synthase kinase-3 beta (Gsk3β), mitogen-activated protein kinases (MAPKs), and the dual-specificity tyrosine-regulated kinase (DYRK) family) [91]. In contrast to MAPKs, in which docking sites are separated from the catalytic sites confer substrate specificity to the enzyme; the specificity and catalytic activity of CDKs depend upon separate protein subunits, called cyclins. Cyclins provide additional sequences required for enzymatic activity [91]. Sequential activation and inactivation of the four distinct members of the CDK family involved in the cell cycle regulation, including CDK4 and CDK6 (during G1), CDK2 (during G1 and S), and CDK1 (during G2 and M), ensure the continuity of the cell cycle [90]. Melatonin exerts a potent inhibitory action on the cell cycle, mainly through the suppression of the expression and also inactivation of the CDKs. In ovarian cancer, melatonin delayed the growth of cancer cells in the G1 phase via the downregulation of the CDK2/4 gene expression. Melatonin treatment of ovarian cancer cell lines resulted in a significant drop in the mRNA and the protein levels of the CDKs, which supported the contention that melatonin may irreversibly arrest the growth of ovarian cancer cells [92]. A similar finding was reported by Liu et al. [77] who showed that 1 mM melatonin could downregulate the expression of CDK4 (related to the G1 phase) and CDK1 (related to G2/M phase) in both protein and mRNA levels in a time-dependent manner. Moreover, there were no significant differences in the levels of CDK2 related to the G1/S transition and the S phase in the hFOB osteosarcoma cell lines [77]. In a later study, the authors reported that the prevention of ERK activation involved a melatonin-induced delay in cell growth in the hFOB cell lines by downregulating the expression of CDK4 and CDK1; this inhibitory effect was potentially mediated via the ERK but not the p38, JNK, or the Akt pathways [78]. Melatonin was also found to inhibit osteosarcoma cell line MG-63 proliferation in a dose-dependent and time-dependent manner via the downregulation of CDK4 and CDK1 [93]. The effects of melatonin on the cell cycle regulatory proteins and the proliferative activity in the mouse model of diethylnitrosamine (DEN)-induced hepatocellular carcinoma were evaluated by Sanchez et al. [94]. They observed that in melatonin plus DEN-treated animals, the expression levels of CDK4 and CDK6 were significantly lowered, but were increased by the highest dose of melatonin used in this study (10 mg/kg). Melatonin was also reported to inhibit the expression levels of CDK4/6 in hepatocarcinoma cell lines [82], CDK2 in neuroblastoma cells [84], and CDK4 in non-small lung cancer cells [95].

4.3. Downregulation of cyclins

Cyclins, a family of approximately 30 proteins, are structurally characterized by the presence of a cyclin box, which is a domain of five α-helices with 100 amino acid residues [96]. The presence of two cyclin boxes, one carboxy-terminal box for the proper folding of the cyclin, and an aminoterminal box for binding to CDK, are common features in many cyclins [96]. In addition, the sequence similarity between cyclins is far less than CDKs. In opposition to CDKs, in which their levels remain stable, cyclins are degraded or synthesized during the cell cycle [97,98]. Cyclin D, including D1, D2, and D3 subtypes are the first members of the cyclin family that sense the mitogenic signals and hence activate CDK4 and CDK6 in the G1 phase [99]. Similarly, the G1/S transition is achieved via the activation of CDK2 by cyclin E1 and E2. During the S phase, cyclin A is degraded and replaced by cyclin E proteins, which leads to the transition from the S phase to mitosis and; finally at the end of the G2 phase, CDK2 interacts with the cyclin B [99]. Melatonin is an oncostatic agent in part due to the exertion of potent anticancer effects through the negative regulation of certain intracellular effectors, such as cell cycle-related gene expression, especially cyclins. Cyclin molecules are targeted by melatonin to inhibit the proliferation of tumor cells. For example, Hong et al. [100] demonstrated that melatonin was a potential chemotherapeutic agent for the treatment of colon cancer, the effects of which were mediated by marked attenuation of E– and A-type cyclins. They showed that melatonin, at a concentration of 10 μM, reduced the expression of cyclin A and cyclin E, but did not affect cyclin D or cyclin B expression. In osteosarcoma, the melatonin's inhibitory effect was reported to be related to the downregulation of cyclin D1 and cyclin B1 [93]. Melatonin showed a dramatic inhibition effect on human osteosarcoma cell proliferation in a dose-dependent and time-dependent manner; this inhibition involved the attenuation of major cell cycle regulators, including cyclin D1 and cyclin B1 [77,93]. The same authors reported, the prevention of ERK activation by the PD98059 (a selective inhibitor of MEK that disrupts downstream activation of ERK) involved a melatonin-induced downregulation of the cyclin in the osteoblastic cell line. They found that the combination of PD98059 and melatonin could synergistically increase the action of either agent alone [78]. Cini et al. [101] reported that the molecular basis for melatonin-induced oncostatic effects was the transcriptional inhibition of the cyclin D1 expression. Due to the key role of the cyclin D1 protein in G1 to S cell cycle transition, it mediates the steroid-dependent growth of both normal and malignant mammary epithelial cells. The results also showed that the suppression of cyclin D1 by estradiol could represent a key molecular event for the cytostatic effect of melatonin in breast cancer cell lines. They found that the melatonin completely abolished the growth advantage exerted by estradiol, while the transfection of the pcDNA3cycD1 plasmid, bearing the human cyclin D1 open reading frame, in turn, completely abolished the antiproliferative activity of melatonin. In this case, melatonin returned the number of cells in the S phase as observed after the addition of only estradiol. Hence, the reinduction of cyclin D1

expression in estradiol-treated cancer cells was abundant to prevent proliferative inhibition. The complex molecular events arising between estradiol addition and the cell cycle stimulation of cancer cells have been demonstrated by melatonin. The induction of the cyclin D1 expression is key step at which melatonin acted to prevent growth-promoting activity of estradiol. Downregulation of the cyclin D1 was also reported to be a mechanism underlying the antiproliferative activity of melatonin in B65 rat dopaminergic neuroblastoma cells [84]. Rögelsperger et al. [102] reported that not only cyclin D1 but also MT1 and the estrogen sulfotransferase SULT1E1 were targeted for the oncostatic action of melatonin in human breast cancer. In prostate cancer, melatonin treatment is associated with further decreases in tumor incidence and growth rate in nude castrated mice. Melatonin and 2-iodomelatonin (a melatonin receptor agonist) attenuated EGF-stimulated rises in cancer cell proliferation and cyclin D1 levels [103]. The mechanism of the antiproliferative effects of melatonin in prostate cancer involved inhibition of the growth of prostate tumors with remarkable decreases in the expression of PCNA, cyclin A, and PSA in the tumors [104]. Employing melatonin as an interesting molecule in controlling cancer development is increasing due to the clinical observations which suggest that melatonin enhances the chemotherapies' efficacies when used in adjuvant settings leading to diminishing side effects [13]. For example, melatonin was reported to enhance the anti-tumor effect of sorafenib in hepatocarcinoma [82], gemcitabine in pancreatic ductal adenocarcinoma [105], all-trans retinoic acid and somatostatin in breast cancer [106], doxorubicin in lung cancer [87], and gefitinib in non-small-cell lung cancer cells [95] along with the down-regulation of cyclin D1, A, and B.

4.4. Upregulation of CDK inhibitors

CDKs activities are regulated by their association with two families of inhibitors including INK4 proteins (p16INK4A, p15INK4B, p18INK4C, and p19INK4D), and the Cip and Kip families (p21CIP1, p27KIP1, and p57KIP2). INK4 inhibitors are responsible for the suppression of CDK4 and CDK6 by blocking their associations with D-type cyclins, whereas Cip and Kip inhibitors suppress the kinase activity of CDK2 and CDK1. CKIs generally function as tumor-suppressors via the restriction of the uncontrolled CDK activity and through the creation of an additional burden on malignant transformation. Melatonin induces the expression of these tumor suppressors. Carbajo-Pescador et al. [107] showed that melatonin induced inhibition on cell proliferation through an alteration in the cell cycle, with an increase in the number of cells in the G2/M phase, and a significant rise in the S phase cell. These increases were achieved with a significant induction in the expression of the p21 protein, which negatively regulated cell cycle progression. In breast cancer, melatonin decreased cell proliferation through an augmentation in the p21wafl expression [108]. Hong et al. [100] suggested that melatonin is a promising chemotherapeutic agent for the treatment of colorectal cancer; the potential effects of melatonin are mediated by the regulation of both cell proliferation and cell death in cancer cells. Melatonin increased the expression of p16 and p21 and thereby inhibited the cell cycle. The inhibitory effects of melatonin on ovarian cancer cell lines were also demonstrated to be mediated by a significant increase in the expression levels of p27KIP1 [92]. The stimulatory effects of melatonin treatment on the p27KIP1 expression were also reported in hepatocarcinoma [82,109], breast cancer [110], prostate cancer [111–113], fibroblast-like synoviocyte [114], hippocampal cells [115], and ovarian follicles [116].

4.5. Upregulation of p53

P53 is an important tumor suppressor gene with a substantial function in cell cycle regulation through the induction of G0/G1 arrest. The p53 protein increases the expression of the p21, which inhibits CDKs, and, therefore, leads to a suppression of the phosphorylation of the retinoblastoma protein (Rb) and subsequent cell cycle arrest. Many studies have investigated the effects of melatonin treatment on the p53 expression and phosphorylation in cancer cells. Mediavilla et al. [108], reported that the concentration of p53 protein in the MCF-7 cells after their incubation in the presence of 1 nM melatonin showed a significant increase in the expression of this nuclear protein. The expression of p21 protein in cells also increased with melatonin treatment. Kim et al. [117] showed that melatonin elevated the expressions of p53, p21, and p27, and hence induced apoptosis in prostate cancer cell lines. Treatment with specific inhibitors of JNK/p38 MAPK demonstrated that the p53-dependent induction of JNK/p38 MAPK directly participates in apoptosis induced by melatonin. In the animal model of hepatoma and also in H22 cell lines, the anti-tumor effects of melatonin were mediated by a rise in the expression levels of p53 [118,119]. In cervical and endometrial cancer cells, Hong et al. [120] showed that at a physiological concentration of melatonin (1 nM), cell proliferation was decreased, mediated by a cell cycle arrest through an increase in the p21 expression, which was mediated by p53. Xu et al. [121] achieved similar results in which melatonin led to a reduction of tumor volume and weight in gastric cancer-bearing mice. Furthermore, melatonin showed a reduction in the Bcl-2 expression and an increase in the expression of Bax, p53, and p21 in the tumor tissue. The results proved that melatonin activated p53 by promoting its accumulation and phosphorylation at Ser15 [122]. This effect resulted in the p53-dependent reduction of cell proliferation and the ability to form colonies in breast cancer cell lines. Melatonin has also the ability to prevent DNA damage accumulation in both normal and transformed cells which requires the efficient phosphorylation of p53 at Ser-15 residue. By employing PD98059 and SB202190, two specific inhibitors of p38 MAPK activity, p53 phosphorylation at Ser-15 was abolished. As a consequence, the melatonin-induced prevention of DNA damage was impaired. Santoro et al. have been emphasized that the activation of the p53 tumor-suppressor pathway may be a critical mediator in the anticancer activity of melatonin [122,123]. Additionally, p53 acetylation is essential for the stabilization and the activation for driving cells to apoptosis/growth inhibition. P53 acetylation is mediated by the overexpression of p300, leading to cell growth arrest by increasing p21 expression. Proietti et al. [124] demonstrated that melatonin drastically downregulated MDM2, which acts as an E3 ubiquitin ligase, promoting the proteasome-dependent p53 degradation, and the inhibited MDM2 shuttling into the nucleus. Melatonin not only induced increases in both the MDMX and p300 levels but also showed simultaneously decreasing Sirt1, a specific inhibitor of p300 activity. As a result, melatonin-treated cells demonstrate significantly higher values of both p53 and acetylated p53. Therefore, melatonin enhanced p53 acetylation by modulating the MDM2/MDMX/p300 pathway. Moreover, the effects of melatonin on the p53 phosphorylation and activation were receptor-dependent. Santoro et al. [125] showed that melatonin triggered p53 phosphorylation through the activation of MT1 and MT2 (as melatonin receptors). Therefore, both chemical inhibition by specific inhibitors such as luzindole and selective gene silencing of the receptors impaired the function of melatonin in triggering p38 phosphorylation and accumulation, consequently, they cause an inhibition of p53 phosphorylation. This was accompanied by a decrease in performance of melatonin in preventing DNA damage and reducing cell proliferation (see Figs. 1 and 2).

5. Melatonin and modulation of apoptosis

In addition to the anti-apoptotic role of melatonin in normal cells, its pro-apoptotic effects in many tumor cells have been extensively studied. Since the amplification of natural and pharmacologically-induced-apoptotic processes are a significant therapeutic feature in cancer treatment, it is not surprising that combination therapy, which integrates conventional therapies with natural molecules to increase their antineoplastic efficacy, has attracted increasing attention. Owing to its pleiotropic functions at physiological and molecular levels, melatonin occupies a prominent position among these compounds. An increasing body of data has demonstrated the significant anticancer effects of melatonin through the induction of major apoptosis pathways in various tumor cells (Table 3). For example, in leukemia HL-60 cell lines, it was reported that melatonin promoted apoptotic events, such as the depolarization of the mitochondrial membrane, the activation of caspases, and the induction of the permeability transition pore [126]. Concerning the stimulatory role of melatonin in the apoptosis of HL-60 cells, it was found that the melatonin treatment of cancer cells resulted in a significant rise in the expression levels of caspase-3 and -9 as major mediators of apoptotic cell death [126,127]. Melatonin's role in the stimulation of apoptosis is not limited to the activation of caspases. Other studies showed that melatonin induces the activation of several members of the Bcl-2 family, such as Bid and Bax in HL-60 cells and this subsequently results in the release of cytochrome *c* from mitochondria [126,128,129]. Melatonin as a tumor suppressor stimulates

Table 2
The functions of melatonin in potentiating the cytotoxic efficacy of various chemotherapeutic agents and natural products.

Cancer type	Concentrations	Chemotherapeutic drug	Target genes	Major finding	Ref.
Lung adenocarcinoma	1–5 mM	Cisplatin	Caspases-3/7	Combination therapy enhanced the apoptotic cell populations through lifting up mitochondrial membrane depolarization, caspases-3/7 activation, and cell cycle arrest induction	[178]
Ewing sarcoma cancer	50 μM–1 mM	Vincristine ifosfamide	Caspase-3, -8, -9, Bid	Melatonin exerts a synergistic antitumor effect with chemotherapeutic drugs on Ewing sarcoma cancer cells through potentiation of the extrinsic apoptotic pathway	[179]
Ovarian cancer	0–2 mM	Cisplatin	P90RSK, HSP27, pERK Caspase-3, PARP	Melatonin augments cisplatin-induced apoptosis through the inactivation of ERK/p90RSK/HSP27 cascade	[180]
Hepatoma	10^{-8}-10^{-5} M	Doxorubicin	Bax Caspase-3 Bcl-2	When combined with Doxorubicin, melatonin substantially increased the effects of cell growth inhibition and cell apoptosis	[181]
Rat pancreatic tumor	1 mM	5-FU, cisplatin, doxorubicin	N/A	Melatonin enhances chemotherapy-induced cytotoxicity and apoptosis	[182]
Prostate cancer	1 mM	Doxorubicin, docetaxel, etoposide	Bcl-2, TRAF-2, hrTNF-alpha, TNF	Melatonin increased the sensitivity of prostate cancer cells to apoptosis	[183]
Hepatocellular carcinoma	10^{-3} M	Doxorubicin	P-AKT, Survivin, CHOP	Melatonin reduces ER stress-induced resistance to doxorubicin in human hepatocellular carcinoma cells via down-regulating the PI3K/AKT pathway	[184]
Glioma	1 mM	TRAIL	Bcl-2, survivin, Akt	Melatonin overcome glioma cell resistance to TRAIL through a PKC/Akt depending on the mechanism	[185]
Cervical cancer	1 mM	5-FU, cisplatin, doxorubicin	Caspase-3	Melatonin makes sensitive human cervical cancer HeLa cells to cisplatin-induced cytotoxicity and apoptosis	[186]
Non-Small-Cell Lung Cancer	0–10 mM	Gefitinib	Caspase-3, Bcl-2, Bcl-xL and survivin, p-EGFR, pAKT	Melatonin acts as a potent chemotherapeutic agent by sensitizing to gefitinib TKI-resistant H1975 cells	[95]
Hepatocellular carcinoma	0-10^{-3} mM	Tunicamycin	CHOP Bcl-2/Bax, COX-2	Melatonin makes sensitive human hepatoma cells to ER stress-induced apoptosis through down-regulating COX-2 expression, increasing the levels of CHOP, and decreasing the Bcl-2/Bax ratio	[187]
Breast cancer	1 mM	Tunicamycin	COX-2, p65, p38 Bim	Melatonin augments antitumor effect via up-regulation of Bim expression and down-regulation of COX-2 expression	[188]
Leukemia	0.01–10 mM	Puromycin	Bcl-2, bcl-xL, caspase-3, PARP, p-AMPK	Melatonin potentiates puromycin-induced apoptosis with caspase-3 and AMPK activation	[189]
Pancreatic ductal adenocarcinoma	3 mM	Gemcitabine	Cyclin D1, MMP-2, MMP-9, CXCR-4, Bcl-xL, VEGF-C, IkB-a	Melatonin overcomes gemcitabine resistance by abrogating nuclear factor-jB activation	[105]
Hepatocellular carcinoma	1 mM	Sorafenib	Mitofusin-2, PARP and BAX	Melatonin increases the sensitivity of human hepatocellular carcinoma cells to sorafenib through induction of apoptosis	[190]
Colon cancer	1 mM	5-FU	Cyclin D1, cyclin E2, CDK2 and CD, K4 PARP, caspase-7, caspase-9	Melatonin synergizes the chemotherapeutic effect of 5-fluorouracil in colon cancer through suppressing PI3K/AKT and NF κB/iNOS signaling pathways	[191]
Hepatocellular carcinoma	1 mM	Cisplatin	Bcl-2, p-IKKα/β, NF-κB p50/p65, COX-2, PARP, caspase-9	Melatonin makes sensitive the cisplatin-mediated growth suppression of cells by inactivating of NF-κB/COX-2 and AP-2β/hTERT signaling	[82]
Lung Cancer, Laryngeal Cancer	0.1 mM or 1.0 mM	Doxorubicin	N/A	Melatonin intensified cytotoxicity of Doxorubicin, significantly decreasing cell numbers and promoting apoptosis	[192]
Breast Cancer	0.3 mM	Doxorubicin	TRPV1, caspases-3, -9, PARP	Melatonin sensitizes the effects of doxorubicin by activation of TRPV1 and apoptosis	[193]
colon cancer	1.0 mM	Flavone	Bcl-XL	Melatonin potentiates flavone-induced apoptosis in human colon cancer cells via increasing the level of glycolytic end products	[194]
Natural products promyelocytic leukemia	1.0 mM	Hydrogen peroxide	Caspases-3, -8, -9	Melatonin enhances hydrogen peroxide-induced apoptosis through enhancing mitochondrial disruption	[195]
Breast Cancer	1 nM	Vitamin D3	TGFb-1, Smad4, Akt, MDM2	Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFb-1-dependent apoptosis	[196]
Breast cancer	2 mM	Arsenic trioxide	Redd1, JNK, and p38, PARP, Survivin, Bax, and Bcl-2.	Melatonin enhances -induced cell death through sustained upregulation of expression in cells	[197]

apoptosis in other ways as well. For example, in RAMOS-1 lymphoblastic cells, melatonin reduced the mitochondrial transmembrane potential which triggered the mitochondrial transition pore and led to the release of cytochrome *c*, promoting the apoptotic cascade, and reducing the induction of the proto-oncogene Bcl-2 [127]. In addition, in an in vitro study using MDA-MB-361 breast cancer cells; it was found that in addition to the release of cytochrome *c* and stimulation of caspase-3 and -9, melatonin enhanced the expression of the Apaf-1 protein. Apaf-1 is a signaling protein that has an important function in the activation of caspase-9 in the presence of cytochrome *c*, subsequently leading to the induction of apoptosis [130,131]. Despite extensive studies on the role of melatonin in the induction of apoptosis, the signaling pathway through which melatonin induces apoptosis, has not been extensively studied. In prostate cancer cells (LNCaP), it was demonstrated that melatonin caused the activation of two major mammalian mitogen-activated protein kinases (MAPK), including p38, and extracellular signal-regulated kinase (ERK), thereby triggering apoptosis in cancer cells. Activation of p38 and the ERK pathway increase apoptotic proteins including Bax and Bad, and subsequently cytochrome *c* and caspase-9, while decreasing the anti-apoptotic proteins Bcl-2 [132,133]. Three members of the MAPK family, including JNK 1, -2, and -3, were up-regulated by melatonin treatment in hepatocarcinoma HepG2 cells. It has been well known that the activation of the JNK signaling pathway is a regular mediator of cell death and induces apoptosis in the hepatic cell. This upregulated the expression of the pro-apoptotic Bcl-2 family, such as Bax, subsequently leads to the releasing of cytochrome *c* and the activation of caspase-8 and -9 [83,134]. After the exposure of HepG2 cells to melatonin, melatonin induces apoptosis through an increase in the expression of the pro-apoptotic protein Bim, mediated by the activation and the nuclear translocation of the FoxO3a transcription factor. Melatonin stabilizes the phosphorylation of FoxO3a in serine/threonine sites and subsequently modulates nuclear localization. Therefore, FoxO3a exerts tumor suppressor functions through the enhanced transcription of pro-apoptotic genes such as the Bim and the Fas ligand [135]. Melatonin also overcomes apoptosis resistance in HepG2 cells by targeting Survivin and XIAP through the COX-2/PI3K/AKT signaling pathway. It is proven that the inhibitor of apoptosis protein (IAPs) families, such as c-IAP-1, c-IAP-2, Survivin, and XIAP perform critical functions in the development of apoptosis resistance. The overexpression of the IAPs family is related to the COX-2 expression; COX-2 is chronically overexpressed in many cancers and has been shown to upregulate PI3K/AKT signaling. It is well known that the activation of PI3K/AKT plays a critical role in resistance to apoptosis by increasing the cellular levels of Survivin and XIAP [136–138]. Melatonin was reported to overcome apoptosis resistance by lowering the expression of COX-2 [139]. In addition, during the definition of the signaling pathways involved in the stimulatory effects of melatonin on apoptosis, it was shown that melatonin decreased cell viability and increased apoptosis in SGC7901 gastric cancer cells. This finding suggested that melatonin inhibited the translocation of NF-κB to the nucleus [140]. In a study that was performed on the colorectal cancer cell line (LoVo cells), it became apparent that melatonin played an important role in controlling apoptosis via the epigenetic alternation in cancer cells. Histone deacetylases (HDACs) have an important role to play in epigenetic

Table 3
The effects on melatonin in apoptosis induction in various cancers.

Cancer type	Melatonin Concentration.	Target genes	Major finding	Ref.
Hepatoma		Survivin, XIAP, COX-2 and AKT	Melatonin overcomes apoptosis resistance by targeting Survivin, XIAP, and is COX-2/PI3K/AKT-dependent	[139]
Colorectal cancer	0.1–2 mM	CaMKII, histone H3, bcl-2, bax, caspase-3,	Melatonin can induce apoptosis of cells through HDAC4 nuclear import mediated via CaMKII inactivation	[141]
Gastric cancer	4 mM	P38, JNK, ERK, caspase-3, Bax bcl-2, p65	Melatonin induced apoptosis via activating the caspase-dependent apoptotic pathway and inhibiting the nuclear translocation of NF-κB p65, these processes are regulated through p38 and JNK	[198]
Ovarian cancer	200 mg/100 g	P53, BAX, caspase-3, Bcl-2, survivin	Melatonin induced apoptosis by modulating the expression levels of pro- and anti-apoptotic proteins	[199]
Hepatoblastoma	50–2000 μM	Bim, FoxO3a	Melatonin can induce apoptosis by upregulating of Bim that mediated through nuclear translocation and activation of the FoxO3a	[135]
Breast cancer	1 mM	P53, p73, MDM2, caspases-9, -7, -6, PARP, Bcl-2, Bax, AIF	Two separate apoptotic processes are triggered by melatonin: an early, TGFb1 and caspase-independent response, and a late apoptotic TGFb1-dependent process in which activated-caspase-7	[200]
Lung adenocarcinoma	0.5–10 mM	HDAC1, histone H3, PUMA, Bax, PCNA, Bcl2	HDAC1 inhibition by melatonin leads to suppression cancer cells through induction of oxidative stress and activation of apoptotic pathways	[201]
Neuroblastoma cancer	1 mM	Caspase-3	Melatonin induced apoptosis through the classical pathway, which involves caspase-3 activation	[202]
Prostate cancer	0–3 mM	Caspase-3, Bax, cytochrome *c*, Bcl-2, p38, JNK	Melatonin induces apoptotic death via p38 and JNK pathways	[132]
Pancreatic carcinoma	10^{-8} -10^{-12} M	Bcl-2/Bax, caspase-9	Melatonin can induce pro-apoptotic pathways via interaction with the Mel-1 A/B receptors	[203]
Cholangiocarcinoma	0.5–2 mM	Caspase-3, -7	Melatonin can induce apoptosis in cholangiocarcinoma cell lines via activating the reactive oxygen species-mediated mitochondrial pathway	[204]
Lung adenocarcinoma	1 pM to 10 mM	Caspase-3, -7	High melatonin concentration exerted anti-cancer effects via changing biomolecular structure of lipids, nucleic acids and proteins, supporting its enhancement of apoptotic induction.	[205]
Leukemia	0.5–1 mM	Caspase-3, -9, Bax/Bcl-2	Melatonin can reduce the viability of cancer cells by induction of apoptosis primarily via regulation of Bax/Bcl-2 expression.	[129]
Lymphoma	0.5–2 mM	Caspase 3, PARP, BCL2, MCL1	Melatonin can inhibit cell proliferation and can induce caspase activation and apoptosis	[206]
Lymphoma	2 mM	Bcl-2, caspase-3	Melatonin provokes cell death by mitochondrial-dependent apoptotic pathway activation	[127]
Breast cancer	1 mM	COX-2, p300, Akt, Apaf-1,	Melatonin inhibits the proliferation and induction of apoptosis through modulation of COX-2, p300, Akt, and Apaf-1 signaling	[130]
Gastric cancer	0.02 M	Caspase-3	Melatonin can inhibit cell proliferation, colony formation and migration efficiency, and it promotes apoptosis	[207]

MDM2, murine double minute 2; PARP, poly ADP ribose polymerase; AIF, apoptotic inducing factor; MCL1, myeloid leukemia 1 XIAP, X-linked inhibitor of apoptosis protein; cox-2, cyclooxygenase-2; JNK, c-Jun N-terminal kinases; HDAC1, Histone Deacetylase 1.

modulation by the deacetylation of histone or non-histone substrates [138]. Melatonin indirectly induced the dephosphorylation and the nuclear translocation of HDAC4. This indirect effect mediated the Ca2+/calmodulin-dependent protein kinase II alpha (CaMKIIα). Hence, melatonin inhibited HDAC4 phosphorylation by CaMKIIα, reduced the phosphorylation of HDACs, leading to nuclear translocation of the enzyme, and removing the acetyl group from the histone comprising the nucleosome. This deacetylation plays an important role in the transcriptional repression of anti-apoptotic proteins such as Bcl-2 [141]. Melatonin is functionally important in the induction of apoptosis but this effect can be significantly amplified when melatonin is combined with other substances. Kahweol (coffee-specific furan diterpene) in combination with melatonin induces apoptosis via another means. Kahweol exhibits wide anti-carcinogenic, anti-inflammatory, and antitumor properties. The co-treatment of Caki cells with melatonin and Kahweol lead to the endoplasmic reticulum (ER) mediated induction of apoptosis and increases in the C/EBP homologous protein (CHOP) expression which acts in the upstream of PUMA and stimulates the induction of this protein. Thus, melatonin synergistically enhanced Kahweol-mediated apoptosis by PUMA upregulation; however, the single treatment of Caki cells with melatonin or Kahweol did not

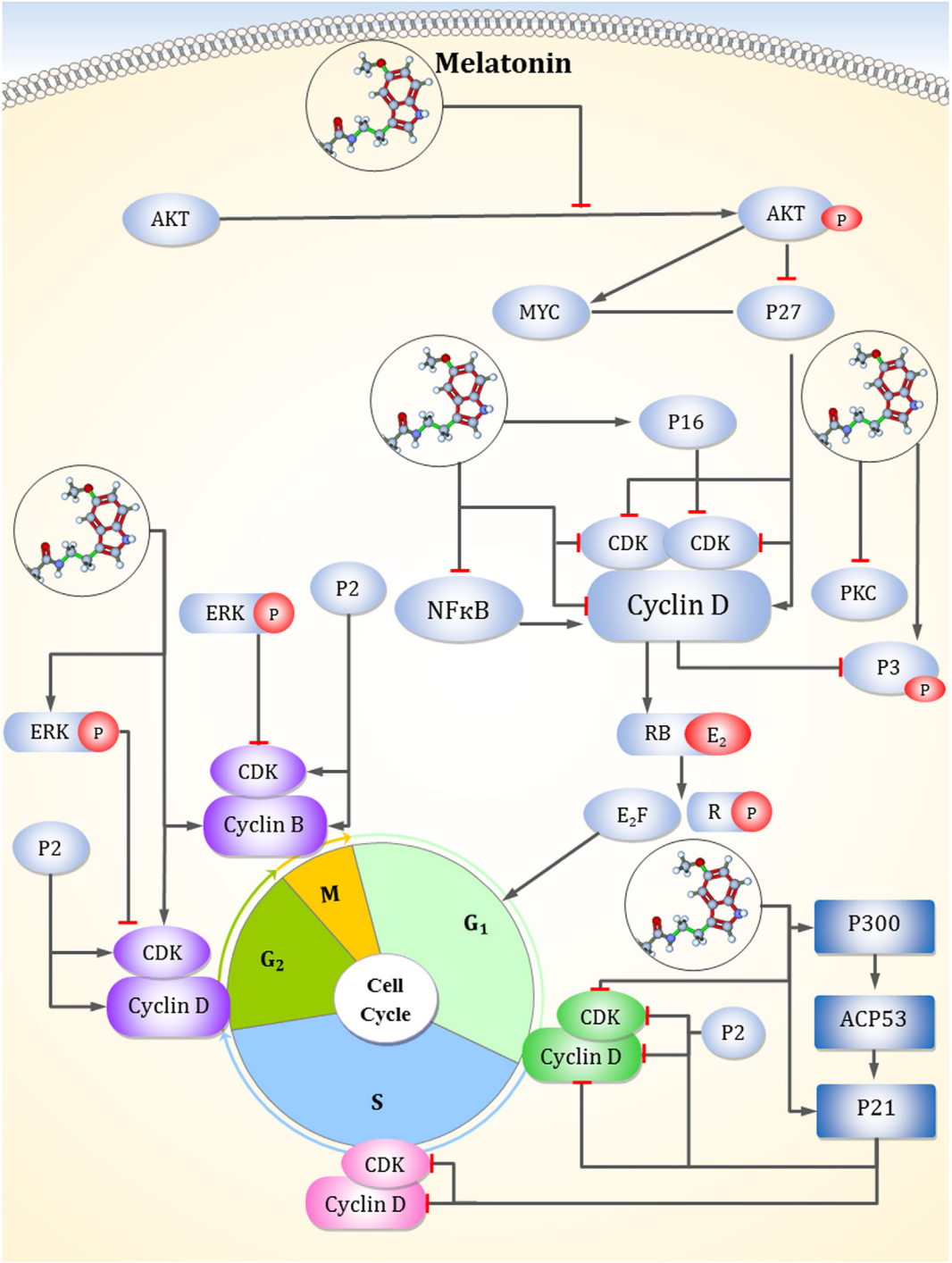

Fig. 1. The schematic view of the cell cycle regulation via melatonin. Melatonin can inhibit many of the factors that contribute to the progress of the cell cycle.

induce ER stress [102,142]. Finally, the combination of melatonin and 5-fluorouracil (5-FU), a chemotherapeutic agent that inhibits thymidylate synthase, dramatically enhanced caspase activation by 5-FU [143]. These findings provide new insights for the treatment of cancer based on a combination of substances or drugs (Table 2)..

6. Melatonin and autophagy

Autophagy or cellular self-digestion is a cellular process that plays an important function in protein and organelle degradation. It is necessary for the protection of cellular hemostasis and the coordination of cellular responses to stress. There are three kinds of autophagy including macroautophagy, microautophagy, and chaperone-mediated autophagy. Among these, macroautophagy is thought to be the dominant type of autophagy. Limitations in nutrients, such as amino acids, growth factors, oxygen, and energy, are involved in autophagy induction. Autophagic defects have been implicated in various diseases including neurodegeneration, aging, infection, and cancer [144]. The role of autophagy in cancer is complex; it contributes to tumor suppression during cancer development through the promotion of cell death but also appears to be oncogenic because of cell death prevention [145,146]. Melatonin has an important function in the modulation of autophagy via the targeting of multiple proteins involved in autophagy; however, its exact function in the regulation of autophagy is poorly understood. Any alteration in this degradative system leads to the intracellular accumulation of misfolded proteins or damaged organelles, thereby leading to pathological malignancy and diseases. Multiple proteins are involved in the development and the progression of autophagy. Melatonin treatment of various cell lines affects these proteins and accordingly leads to autophagy. The mammalian target of the rapamycin complex 1 (mTORC1) is an important potential inhibitor of autophagy in all eukaryotes [147–149]. mTORC1 inhibits the autophagy-initiating ULK complex by phosphorylating complex components, including autophagy-related gene 13 (ATG13); ULK1/2, the ULK1 complex (including ULK1, Atg13, FIP200, Atg101) is also activated and translocated to a specific domain of the endoplasmic reticulum that initiates autophagosome formation [150]. The inhibition of phosphorylation by mTOR can induce autophagy. Melatonin inhibits phosphorylation of the ULK1/2 complex protein through the mTOR signaling pathway [151,152]. Microtubule-associated protein 1 light chain 3 (LC3) is also a crucial mediator and effector of autophagy and is required for autophagosome formation. The treatment of corneal fibroblast cells with melatonin increased the LC3 II and the LC3 punta formation. Using this mechanism, melatonin could subsequently induce autophagy [151,153]. Beclin-1 is a mammalian ortholog of the yeast autophagy-related gene 6 (Atg6). This factor has a central role in the induction of autophagy. Beclin-1 has a vital role in phagosome maturation. This process occurs after binding Beclin-1 with hVps34/class III phosphatidylinositol-3-kinase [154,155]. The administration of melatonin increased the expression of Beclin-1 and subsequently induced autophagy [156,157]. More recently, a study revealed that melatonin synergized with doxorubicin causes apoptosis of breast cancer cells by reducing the expression of AMP-activated protein kinase α1 (AMPK α1), which performs as a necessary survival factor for cancer cells. This cotreatment-induced decrease in AMPKα1 expression appeared at the transcriptional level via an autophagy-dependent mechanism [158,159]. Via these pathways, they are likely major strategies by which melatonin induces autophagy.

7. Melatonin and mitochondrial

Mitochondria are organelles with multifunctional ability implicated in basically all cellular activity such as apoptosis,

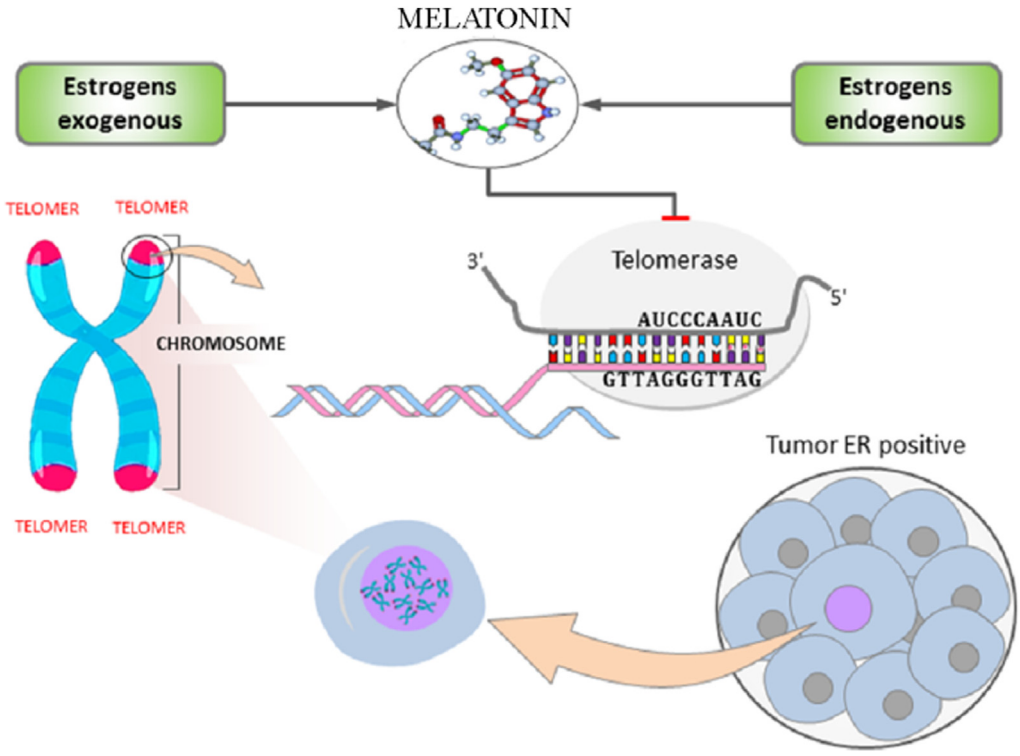

Fig. 2. The schematic represents shows that melatonin can inhibit telomerase activity through down-regulating hTERT (catalytic subunit of telomerase), this action is facilitated by endogenous and exogenous estrogens.

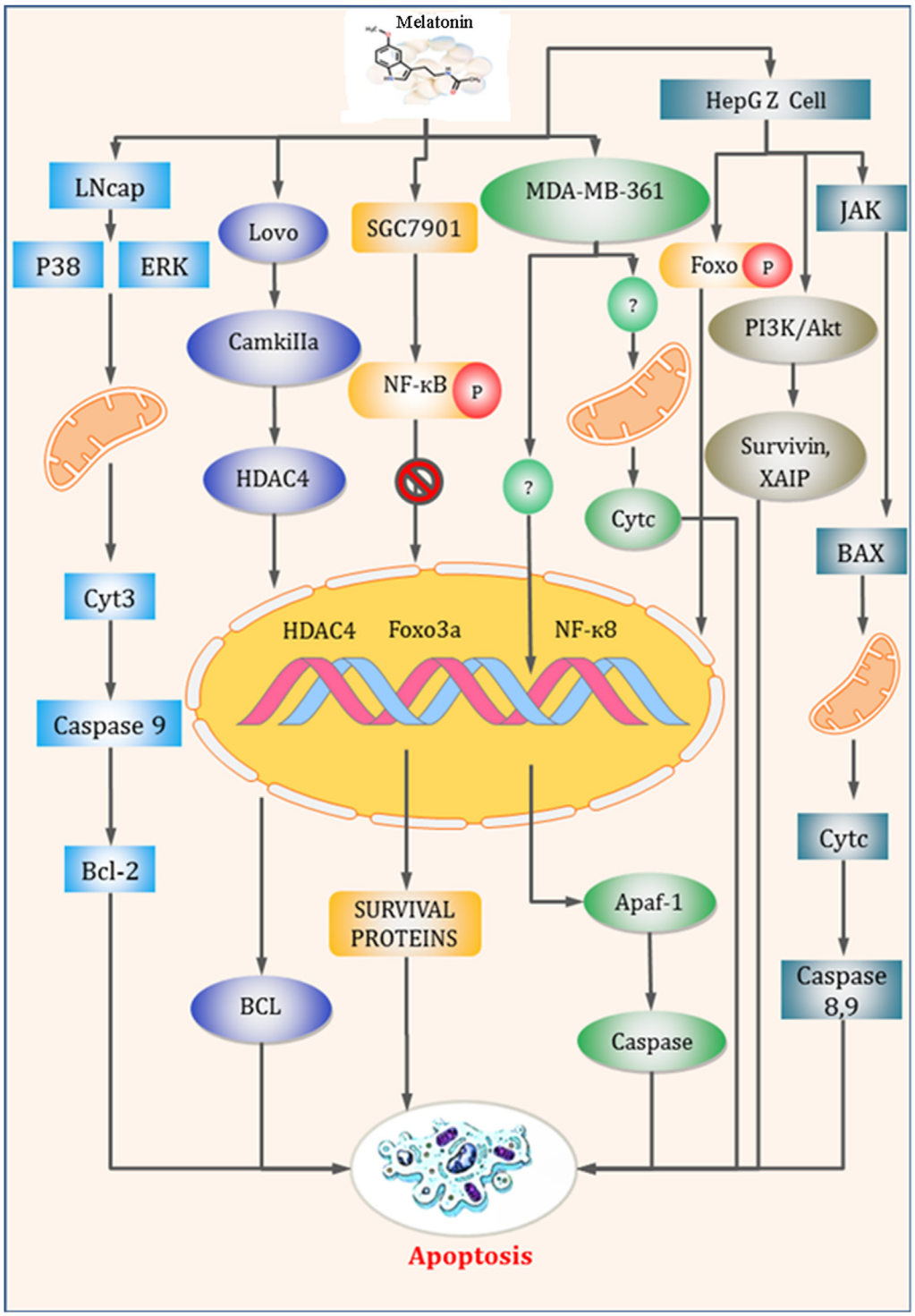

Fig. 3. The schematic diagram shows the role of melatonin in the modulation of apoptosis, melatonin exerts pro-apoptotic action in several cell lines by affecting multiple signaling pathways and proteins.

autophagy, energy production and glucose metabolism [160]. The current finding of melatonin in mitochondria of normal cells and its synthesis in these organelles contribute to restraining ROS defeat as melatonin instantly scavenges ROS and also promotes antioxidant enzyme expression [161]. Several studies have demonstrated the capacity of melatonin to decline damage to key mitochondrial components including the mitochondrial genome and proteins of the electron transport chain, which usually occurs under situations of high oxidative stress. By upregulation of SIRT3 as the major mitochondrial deacetylase, melatonin's promote mitochondrial superoxide dismutase 2 (SOD2) and its deacetylation signaled [162].

Melatonin provokes glutathione, a different antioxidant that diminishes electron leakage from the mitochondrial electron chain. In combination with sorafenib, melatonin synergistically impeded the growth of PDAC cells and affected mitochondrial-mediated

apoptosis through inhibition of the platelet-derived growth factor-β (PDGFR-β)/STAT3 pathway and MT-mediated STAT-3 [163].

The anti-apoptotic impact of melatonin interrupted with PI3K/AKT via an intrinsic mitochondrial pathway in a caspase-dependent way. In line with previous studies, Yang et al. demonstrated that melatonin treatment reduced cytochrome *c* release from mitochondria and diminished caspase-3 and caspase-9 activation. Further, melatonin reduces caspase-3 and caspase-9 activities, which are assembled through the inhibition of both Bax and mPTP activation. Likewise, melatonin treatment has been described to repress the activation of caspase-3, which impacts the cell cycle G2/M phase arrest [164]. Moreover, melatonin can be taken up from the systemic circulation by mitochondria even can be synthesized by these organelles.

8. Conclusions

Melatonin has oncostatic activity due to a variety of biological processes including antiproliferative actions, the stimulation of anti-cancer immunity, the modulation of the cell cycle, apoptosis, the modulation of oncogene expression, and antiangiogenic effects. Melatonin's inhibitory effects have been assessed in many cell culture lines and experimental animal models [165]. Relative to breast cancer, studies performed using in the MCF-7 cells have shown that the use of melatonin in combination with estradiol inhibits cell proliferation [165]. The stimulation of apoptosis may be an important strategy for anticancer therapy. Melatonin, along with retinoic acid, inhibits cell growth and decreases the number of cells via apoptosis activation in MCF-7 hormone-dependent breast cancer cells [166]. Melatonin, in combination with somatostatin, not only exerts antiproliferative effects but also enhances apoptosis of murine colon-38 cancer cells [167]. Many reports have shown that melatonin modulates the efficacy of chemotherapeutic agents. The results revealed that melatonin can elevate the antitumor activity of tamoxifen in several types of metastatic cancers (hepatocellular carcinoma, cervix carcinoma, uterine cancer, pancreatic cancer, breast cancer, ovarian cancer, and non-small cell lung cancer) [168–170]. It was known that the administration of melatonin, in combination with tamoxifen, may affect the clinical regression of cancer in women with metastatic breast cancer [46]. The clinical studies of patients with non-small cell lung carcinoma have reported that the use of melatonin along with cisplatin and etoposide elevates the survival rate by about five years [171]. The evidence is strong that melatonin can be used as an adjuvant in cancer therapy. Melatonin is beneficial in cancer therapy, while melatonin may not adequate as a sole cancer therapy; it seems likely that it would be highly effective as an adjunctive in cancer treatment.

Ethical code

This study was approved by the Ethics Committee of Golestan University of Medical Sciences, Gorgan, Iran (code: IR.GOUMS.REC.1400.409).

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

SM is grateful to Golestan University of Medical Sciences, Gorgan, Iran, for providing all kinds of facilities to prepare this manuscript.

References

[1] R.J. Reiter, S. Rosales-Corral, D.X. Tan, M.J. Jou, A. Galano, B. Xu, Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas, Cell. Mol. Life Sci. 74 (2017) 3863–3881.
[2] B. Jung, N. Ahmad, Melatonin in cancer management: progress and promise, Cancer Res. 66 (2006) 9789–9793.
[3] S.R. Pandi-Perumal, I. Trakht, V. Srinivasan, D.W. Spence, G.J. Maestroni, N. Zisapel, D.P. Cardinali, Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways, Prog. Neurobiol. 85 (2008) 335–353.
[4] F. Luchetti, B. Canonico, M. Betti, M. Arcangeletti, F. Pilolli, M. Piroddi, L. Canesi, S. Papa, F. Galli, Melatonin signaling and cell protection function, Faseb. J. 24 (2010) 3603–3624.
[5] J.D. Johnston, D.J. Skene, 60 years OF neuroendocrinology: regulation of mammalian neuroendocrine physiology and rhythms by melatonin, J. Endocrinol. 226 (2015) T187–T198.
[6] R.J. Reiter, J.C. Mayo, D.X. Tan, R.M. Sainz, M. Alatorre-Jimenez, L. Qin, Melatonin as an antioxidant: under promises but over delivers, J. Pineal Res. 3 (61) (2016) 253–278.
[7] S. Mańka, E. Majewska, Immunoregulatory action of melatonin. The mechanism of action and the effect on inflammatory cells, Postępy Higieny Medycyny Doświadczalnej 70 (2016) 1059–1067.
[8] S. Proietti, A. Cucina, M. Minini, M. Bizzarri, Melatonin, Mitochondria, and the Cancer Cell, Cellular and Molecular Life Sciences, 2017, pp. 1–11.
[9] S. Proietti, A. Cucina, M. Minini, M. Bizzarri, Melatonin, mitochondria, and the cancer cell, Cell. Mol. Life Sci. 74 (2017) 4015–4025.
[10] G. Di Bella, F. Mascia, L. Gualano, L. Di Bella, Melatonin anticancer effects, Int. J. Mol. Sci. 14 (2013) 2410–2430.
[11] P. Lissoni, Melatonin in Human Cancer: Therapeutic Possibilities, Melatonin and Melatonergic Drugs in Clinical Practice, Springer, 2014, pp. 43–56.
[12] V. Srinivasan, S. R Pandi-Perumal, A. Brzezinski, K. P Bhatnagar, D. P Cardinali, Melatonin, Immune function and cancer, Recent patents on endocrine, metabolic & immune drug discovery 5 (2011) 109–123.
[13] A. Cutando, J. Aneiros-Fernández, A. López-Valverde, S. Arias-Santiago, J. Aneiros-Cachaza, R.J. Reiter, A new perspective in oral health: potential importance and actions of melatonin receptors MT1, MT2, MT3, and RZR/ROR in the oral cavity, Arch. Oral Biol. 56 (2011) 944–950.
[14] R. Reiter, S. Rosales-Corral, D.-X. Tan, D. Acuna-Castroviejo, L. Qin, S.-F. Yang, K. Xu, Melatonin, a full service anti-cancer agent: inhibition of initiation, progression and metastasis, Int. J. Mol. Sci. 18 (2017) 843.
[15] V. Srinivasan, D.W. Spence, S.R. Pandi-Perumal, I. Trakht, D.P. Cardinali, Therapeutic actions of melatonin in cancer: possible mechanisms, Integr. Cancer Ther. 7 (2008) 189–203.
[16] R.J. Reiter, Mechanisms of cancer inhibition by melatonin, J. Pineal Res. 37 (2004) 213–214.
[17] C.R. Vijayalaxmi, Thomas Jr., R.J. Reiter, T.S. Herman, Melatonin: from basic research to cancer treatment clinics, J. Clin. Oncol. 20 (2002) 2575–2601.
[18] A.Z. Chiru, C. Popescu, D. Gheorghe, Melatonin and cancer, J. Med. Life 7 (2014) 373.
[19] S. Cos, A. González, C. Martínez-Campa, M.D. Mediavilla, C. Alonso-González, E.J. Sánchez-Barceló, Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions, Cancer Detect. Prev. 30 (2006) 118–128.
[20] E.J. Sánchez-Barceló, S. Cos, D. Mediavilla, C. Martínez-Campa, A. González, C. Alonso-González, Melatonin–estrogen interactions in breast cancer, J. Pineal Res. 38 (2005) 217–222.
[21] G. Maestroni, A. Conti, Melatonin in human breast cancer tissue: association with nuclear grade and estrogen receptor status, Laboratory investigation, a journal of technical methods and pathology 75 (1996) 557–561.
[22] A.G. Rato, J.G. Pedrero, M.A. Martínez, B. Del Rio, P.S. Lazo, S. Ramos, Melatonin blocks the activation of estrogen receptor for DNA binding, Faseb. J. 13 (1999) 857–868.
[23] S. Proietti, A. Cucina, R.J. Reiter, M. Bizzarri, Molecular mechanisms of melatonin's inhibitory actions on breast cancers, Cell. Mol. Life Sci. 70 (2013) 2139–2157.
[24] B. del Río, J.M.G. Pedrero, C. Martínez-Campa, P. Zuazua, P.S. Lazo, S. Ramos, Melatonin, an endogenous-specific inhibitor of estrogen receptor α via calmodulin, J. Biol. Chem. 279 (2004) 38294–38302.
[25] S. Cos, A. González, C. Martínez-Campa, M. Mediavilla, C. Alonso-González, E. Sánchez-Barceló, Melatonin as a selective estrogen enzyme modulator, Curr. Cancer Drug Targets 8 (2008) 691–702.
[26] A. Gonzalez, S. Cos, C. Martinez-Campa, C. Alonso-Gonzalez, S. Sanchez-Mateos, M. Mediavilla, E. Sanchez-Barcelo, Selective estrogen enzyme modulator actions of melatonin in human breast cancer cells, J. Pineal Res. 45 (2008) 86–92.
[27] M.M. Leon-Blanco, J.M. Guerrero, R.J. Reiter, J.R. Calvo, D. Pozo, Melatonin inhibits telomerase activity in the MCF-7 tumor cell line both in vivo and in vitro, J. Pineal Res. 35 (2003) 204–211.
[28] S.E. Artandi, R.A. DePinho, Telomeres and telomerase in cancer, Carcinogenesis 31 (2010) 9–18.
[29] R. Jahanban-Esfahlan, K. Seidi, A. Monfaredan, V. Shafie-Irannejad, M.M. Abbasi, A. Karimian, B. Yousefi, The herbal medicine Melissa officinalis extract effects on gene expression of p53, Bcl-2, Her2, VEGF-A and hTERT in

human lung, breast and prostate cancer cell lines, Gene 613 (2017) 14–19.
[30] C.M. Martínez-Campa, C. Alonso-González, M.D. Mediavilla, S. Cos, A. González, E.J. Sanchez-Barcelo, Melatonin down-regulates hTERT expression induced by either natural estrogens (17β-estradiol) or metalloestrogens (cadmium) in MCF-7 human breast cancer cells, Cancer Lett. 268 (2008) 272–277.
[31] C. Karaaslan, S. Suzen, Antioxidant properties of melatonin and its potential action in diseases, Curr. Top. Med. Chem. 15 (2015) 894–903.
[32] R. Hardeland, Melatonin's Antioxidant Properties: Molecular Mechanisms, Melatonin and Melatonergic Drugs in Clinical Practice, Springer, 2014, pp. 17–26.
[33] D.-X. Tan, L.C. Manchester, E. Esteban-Zubero, Z. Zhou, R.J. Reiter, Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism, Molecules 20 (2015) 18886–18906.
[34] J. Welti, S. Loges, S. Dimmeler, P. Carmeliet, Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer, J. Clin. Invest. 123 (2013) 3190.
[35] S. Carbajo-Pescador, R. Ordonez, M. Benet, R. Jover, A. García-Palomo, J. Mauriz, J. González-Gallego, Inhibition of VEGF expression through blockade of Hif1α and STAT3 signalling mediates the anti-angiogenic effect of melatonin in HepG2 liver cancer cells, Br. J. Cancer 109 (2013) 83.
[36] L.G.D.A. Chuffa, Y.R. Zonta, M. Martinez, I.C.C. Camargo, R.F. Domeniconi, L.A.L. Junior, P.F.F. Pinheiro, R.J. Reiter, F.E. Martinez, Melatonin Reduces Angiogenesis in Serous Papillary Ovarian Carcinoma of Ethanol-Preferring Rats, 2017.
[37] R. Zhou, R. Wang, J. Song, H. Zhang, J. Luo, H. Liu, Melatonin inhibit the angiogenesis of gastric cancer by nuclear receptor, Faseb. J. 29 (2015), 639.635.
[38] Y.R. Zonta, M. Martinez, I.C.C. Camargo, R.F. Domeniconi, L.A. Lupi Júnior, P.F.F. Pinheiro, R.J. Reiter, F.E. Martinez, L.G.A. Chuffa, Melatonin reduces angiogenesis in serous papillary ovarian carcinoma of ethanol-preferring rats, Int. J. Mol. Sci. 18 (2017) 763.
[39] A. González, A. González-González, C. Alonso-González, J. Menéndez-Menéndez, C. Martínez-Campa, S. Cos, Melatonin inhibits angiogenesis in SH-SY5Y human neuroblastoma cells by downregulation of VEGF, Oncol. Rep. 37 (2017) 2433–2440.
[40] E.J. Sohn, G. Won, J. Lee, S. Lee, S.-h. Kim, Upregulation of miRNA3195 and miRNA374b mediates the anti-angiogenic properties of melatonin in hypoxic PC-3 prostate cancer cells, J. Cancer 6 (2015) 19.
[41] A. Ahluwalia, I.M. Brzozowska, A. Szabo, M.K. Jones, A.S. Tarnawski, Su2082 melatonin reverses impaired angiogenesis in aging gastric endothelial cells: first demonstration and characterization of melatonin receptors in gastric endothelial cells and novel mechanistic role of melatonin in angiogenesis and local interactions with VEGF signaling in aging gastric mucosa, Gastroenterology 150 (2016) S630.
[42] J. León, J. Casado, S.M. Jiménez Ruiz, M.S. Zurita, C. González-Puga, J.D. Rejón, A. Gila, P. Muñoz de Rueda, E.J. Pavón, R.J. Reiter, Melatonin reduces endothelin-1 expression and secretion in colon cancer cells through the inactivation of FoxO-1 and NF-κβ, J. Pineal Res. 56 (2014) 415–426.
[43] J. Colombo, J.M.W. Maciel, L.C. Ferreira, R.F. Da Silva, D.A.P.D.C. Zuccari, Effects of melatonin on HIF-1α and VEGF expression and on the invasive properties of hepatocarcinoma cells, Oncol. Lett. 12 (2016) 231–237.
[44] K.J. Kim, J.S. Choi, I. Kang, K.W. Kim, C.H. Jeong, J.W. Jeong, Melatonin suppresses tumor progression by reducing angiogenesis stimulated by HIF-1 in a mouse tumor model, J. Pineal Res. 54 (2013) 264–270.
[45] S. Cos, R. Fernández, A. Güézmes, E.J. Sánchez-Barceló, Influence of melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells, Cancer Res. 58 (1998) 4383–4390.
[46] P. Lissoni, S. Barni, S. Meregalli, V. Fossati, M. Cazzaniga, D. Esposti, G. Tancini, Modulation of cancer endocrine therapy by melatonin: a phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone, Br. J. Cancer 71 (1995) 854.
[47] T.F. Borin, A.S. Arbab, G.B. Gelaleti, L.C. Ferreira, M.G. Moschetta, B.V. Jardim-Perassi, A. Iskander, N.R.S. Varma, A. Shankar, V.B. Coimbra, Melatonin decreases breast cancer metastasis by modulating Rho-associated kinase protein-1 expression, J. Pineal Res. 60 (2016) 3–15.
[48] T. Borin, A. Arbab, L. Ferreira, G. Botaro, L. Maschio, G. Moschetta, N. Gonçalves, G. Martins, D. Zuccari, 522 Evaluation of the Efficacy of Melatonin in Breast Cancer Metastasis Mediated by ROCK-1, European Journal of Cancer, 2014, pp. 169–170.
[49] P. Lissoni, M. Cazzaniga, G. Tancini, E. Scardino, R. Musci, S. Barni, M. Maffezzini, T. Meroni, F. Rocco, A. Conti, Reversal of clinical resistance to LHRH analogue in metastatic prostate cancer by the pineal hormone melatonin: efficacy of LHRH analogue plus melatonin in patients progressing on LHRH analogue alone, Eur. Urol. 31 (1997) 178–181.
[50] R. Ordonez, S. Carbajo-Pescador, N. Prieto-Dominguez, A. García-Palomo, J. González-Gallego, J.L. Mauriz, Inhibition of matrix metalloproteinase-9 and nuclear factor kappa B contribute to melatonin prevention of motility and invasiveness in HepG2 liver cancer cells, J. Pineal Res. 56 (2014) 20–30.
[51] C.-M. Yeh, C.-W. Lin, J.-S. Yang, W.-E. Yang, S.-C. Su, S.-F. Yang, Melatonin inhibits TPA-induced oral cancer cell migration by suppressing matrix metalloproteinase-9 activation through the histone acetylation, Oncotarget 7 (2016) 21952.
[52] Q. Zhou, S. Gui, Q. Zhou, Y. Wang, Melatonin inhibits the migration of human lung adenocarcinoma A549 cell lines involving JNK/MAPK pathway, PLoS One 9 (2014), e101132.
[53] S.-H. Park, L.W. Cheung, A.S. Wong, P.C. Leung, Estrogen regulates Snail and Slug in the down-regulation of E-cadherin and induces metastatic potential of ovarian cancer cells through estrogen receptor α, Mol. Endocrinol. 22 (2008) 2085–2098.
[54] S.C. Su, M.J. Hsieh, W.E. Yang, W.H. Chung, R.J. Reiter, S.F. Yang, Cancer metastasis: mechanisms of inhibition by melatonin, J. Pineal Res. 1 (62) (2016) e12370.
[55] R.J. Reiter, S.A. Rosales-Corral, D.-X. Tan, D. Acuna-Castroviejo, L. Qin, S.-F. Yang, K. Xu, Melatonin, a full service anti-cancer agent: inhibition of initiation, progression and metastasis, Int. J. Mol. Sci. 18 (2017) 843.
[56] A. Carrillo-Vico, P.J. Lardone, N. Álvarez-Sánchez, A. Rodríguez-Rodríguez, J.M. Guerrero, Melatonin: buffering the immune system, Int. J. Mol. Sci. 14 (2013) 8638–8683.
[57] P.J. Lardone, N. Álvarez-Sánchez, A. Rodríguez-Rodríguez, J.M. Guerrero, A. Carrillo-Vico, Multiple Facets of Melatonin in Immunity: Clinical Applications, Melatonin and Melatonergic Drugs in Clinical Practice, Springer, 2014, pp. 117–141.
[58] A. Vinther, M. Claesson, The influence of melatonin on the immune system and cancer, Ugeskr Laeger 177 (2015), V10140568-V10140568.
[59] A. Korkmaz, E.J. Sanchez-Barcelo, D.-X. Tan, R.J. Reiter, Role of melatonin in the epigenetic regulation of breast cancer, Breast Cancer Res. Treat. 115 (2009) 13–27.
[60] A. Korkmaz, R.J. Reiter, Epigenetic regulation: a new research area for melatonin? J. Pineal Res. 44 (2008) 41–44.
[61] B. Brueckner, D. Kuck, F. Lyko, DNA methyltransferase inhibitors for cancer therapy, Cancer J. 13 (2007) 17–22.
[62] M. Ducasse, M.A. Brown, Epigenetic aberrations and cancer, Mol. Cancer 5 (2006) 60.
[63] A.P. Bird, The relationship of DNA methylation to cancer, Cancer Surv. 28 (1995) 87–101.
[64] R. Sharma, T. Ottenhof, P.A. Rzeczkowska, L.P. Niles, Epigenetic targets for melatonin: induction of histone H3 hyperacetylation and gene expression in C17. 2 neural stem cells, J. Pineal Res. 45 (2008) 277–284.
[65] Y. Pan, L.P. Niles, Epigenetic mechanisms of melatonin action in human SH-SY5Y neuroblastoma cells, Mol. Cell. Endocrinol. 402 (2015) 57–63.
[66] L.P. Niles, Y. Pan, S. Kang, A. Lacoul, Melatonin induces histone hyperacetylation in the rat brain, Neurosci. Lett. 541 (2013) 49–53.
[67] L. Agez, V. Laurent, P. Pevet, M. Masson-Pévet, F. Gauer, Melatonin affects nuclear orphan receptors mRNA in the rat suprachiasmatic nuclei, Neuroscience 144 (2007) 522–530.
[68] H.T. Park, S.Y. Baek, B.S. Kim, J.B. Kim, J.J. Kim, Developmental expression of 'RZRβ, a putative nuclear-melatonin receptor'mRNA in the suprachiasmatic nucleus of the rat, Neurosci. Lett. 217 (1996) 17–20.
[69] H. Chen, R.J. Lin, W. Xie, D. Wilpitz, R.M. Evans, Regulation of hormone-induced histone hyperacetylation and gene activation via acetylation of an acetylase, Cell 98 (1999) 675–686.
[70] E.R. Lee, K.W. McCool, F.E. Murdoch, M.K. Fritsch, Dynamic changes in histone H3 phosphoacetylation during early embryonic stem cell differentiation are directly mediated by mitogen-and stress-activated protein kinase 1 via activation of MAPK pathways, J. Biol. Chem. 281 (2006) 21162–21172.
[71] G. Benıtez-King, M.a.E. Hernández, R. Tovar, G. Ramırez, Melatonin activates PKC-α but not PKC-ε in N1E-115 cells, Neurochem. Int. 39 (2001) 95–102.
[72] Ü. Kilic, E. Kilic, R.J. Reiter, C.L. Bassetti, D.M. Hermann, Signal transduction pathways involved in melatonin-induced neuroprotection after focal cerebral ischemia in mice, J. Pineal Res. 38 (2005) 67–71.
[73] S. Keshavarzi, M. Salehi, F. Farifteh-Nobijari, T. Hosseini, S. Hosseini, A. Ghazifard, M. Ghaffari Novin, V. Fallah-Omrani, M. Nourozian, A. Hosseini, Melatonin modifies histone acetylation during in vitro maturation of mouse oocytes, Cell J. 20 (2018) 244–249.
[74] S. Cos, D.E. Blask, A. Lemus-Wilson, A.B. Hill, Effects of melatonin on the cell cycle kinetics and "estrogen-rescue" of MCF-7 human breast cancer cells in culture, J. Pineal Res. 10 (1991) 36–42.
[75] S. Cos, J. Recio, E. Sanchez-Barcelo, Modulation of the length of the cell cycle time of MCF-7 human breast cancer cells by melatonin, Life Sci. 58 (1996) 811–816.
[76] J. Cabrera, G. Negrín, F. Estévez, J. Loro, R.J. Reiter, J. Quintana, Melatonin decreases cell proliferation and induces melanogenesis in human melanoma SK-MEL-1 cells, J. Pineal Res. 49 (2010) 45–54.
[77] L. Liu, Y. Zhu, Y. Xu, R.J. Reiter, Melatonin delays cell proliferation by inducing G1 and G2/M phase arrest in a human osteoblastic cell line hFOB 1.19, J. Pineal Res. 50 (2011) 222–231.
[78] L. Liu, Y. Zhu, Y. Xu, R.J. Reiter, Prevention of ERK activation involves melatonin-induced G1 and G2/M phase arrest in the human osteoblastic cell line hFOB 1.19, J. Pineal Res. 53 (2012) 60–66.
[79] M.M. Marelli, P. Limonta, R. Maggi, M. Motta, R. Moretti, Growth-inhibitory activity of melatonin on human androgen-independent DU 145 prostate cancer cells, Prostate 45 (2000) 238–244.
[80] R.M. Moretti, M.M. Marelli, R. Maggi, D. Dondi, M. Motta, P. Limonta, Antiproliferative action of melatonin on human prostate cancer LNCaP cells, Oncol. Rep. 7 (2000) 347–398.
[81] S.Y. Shiu, L. Li, J.N. Xu, C.S. Pang, J.T. Wong, S.F. Pang, Melatonin-induced inhibition of proliferation and G1/S cell cycle transition delay of human choriocarcinoma JAr cells: possible involvement of MT2 (MEL1B) receptor, J. Pineal Res. 27 (1999) 183–192.

[82] F. Long, C. Dong, K. Jiang, Y. Xu, X. Chi, D. Sun, R. Liang, Z. Gao, S. Shao, L. Wang, Melatonin enhances the anti-tumor effect of sorafenib via AKT/p27-mediated cell cycle arrest in hepatocarcinoma cell lines, RSC Adv. 7 (2017) 21342–21351.
[83] J. Martín-Renedo, J.L. Mauriz, F. Jorquera, O. Ruiz-Andrés, P. González, J. González-Gallego, Melatonin induces cell cycle arrest and apoptosis in hepatocarcinoma HepG2 cell line, J. Pineal Res. 45 (2008) 532–540.
[84] J.G. Pizarro, M. Yeste-Velasco, J.L. Esparza, E. Verdaguer, M. Pallàs, A. Camins, J. Folch, The antiproliferative activity of melatonin in B65 rat dopaminergic neuroblastoma cells is related to the downregulation of cell cycle-related genes, J. Pineal Res. 45 (2008) 8–16.
[85] I. Pirozhok, A. Meye, O.W. Hakenberg, S. Füssel, M.P. Wirth, Serotonin and melatonin do not play a prominent role in the growth of prostate cancer cell lines, Urol. Int. 84 (2010) 452–460.
[86] M. Büyükavcı, Ö. Özdemir, S. Buck, M. Stout, Y. Ravindranath, S. Savaşan, Melatonin cytotoxicity in human leukemia cells: relation with its pro-oxidant effect, Fund. Clin. Pharmacol. 20 (2006) 73–79.
[87] N. Song, A.J. Kim, H.J. Kim, H.J. Jee, M. Kim, Y.H. Yoo, J. Yun, Melatonin suppresses doxorubicin-induced premature senescence of A549 lung cancer cells by ameliorating mitochondrial dysfunction, J. Pineal Res. 53 (2012) 335–343.
[88] A. Panzer, M.-L. Lottering, P. Bianchi, D.K. Glencross, J.H. Stark, J.C. Seegers, Melatonin has no effect on the growth, morphology or cell cycle of human breast cancer (MCF-7), cervical cancer (HeLa), osteosarcoma (MG-63) or lymphoblastoid (TK6) cells, Cancer Lett. 122 (1998) 17–23.
[89] K. Vermeulen, D.R. Van Bockstaele, Z.N. Berneman, The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer, Cell Prolif 36 (2003) 131–149.
[90] T. Otto, P. Sicinski, Cell cycle proteins as promising targets in cancer therapy, Nat. Rev. Cancer 17 (2017) 93.
[91] M. Malumbres, Cyclin-dependent kinases, Genome Biol. 15 (2014) 122.
[92] C.-J. Shen, C.-C. Chang, Y.-T. Chen, C.-S. Lai, Y.-C. Hsu, Melatonin suppresses the growth of ovarian cancer cell lines (OVCAR-429 and PA-1) and potentiates the effect of G1 arrest by targeting CDKs, Int. J. Mol. Sci. 17 (2016) 176.
[93] L. Liu, Y. Xu, R.J. Reiter, Melatonin inhibits the proliferation of human osteosarcoma cell line MG-63, Bone 55 (2013) 432–438.
[94] D.I. Sánchez, B. González-Fernández, B. San-Miguel, J.O. Urbina, I. Crespo, J. González-Gallego, M.J. Tuñón, Melatonin prevents deregulation of the sphingosine kinase/sphingosine 1-phosphate signaling pathway in a mouse model of diethylnitrosamine-induced hepatocellular carcinoma, J. Pineal Res. (2017) 62.
[95] M. Yun, E.-O. Kim, D. Lee, J.-H. Kim, J. Kim, H. Lee, J. Lee, S.-H. Kim, Melatonin sensitizes H1975 non-small-cell lung cancer cells harboring a T790M-targeted epidermal growth factor receptor mutation to the tyrosine kinase inhibitor gefitinib, Cell. Physiol. Biochem. 34 (2014) 865–872.
[96] L. Cao, F. Chen, X. Yang, W. Xu, J. Xie, L. Yu, Phylogenetic analysis of CDK and cyclin proteins in premetazoan lineages, BMC Evol. Biol. 14 (2014) 10.
[97] J. Kamenz, J.E. Ferrell, The temporal ordering of cell-cycle phosphorylation, Mol. Cell 65 (2017) 371–373.
[98] S. Lim, P. Kaldis, Cdks, cyclins and CKIs: roles beyond cell cycle regulation, Development 140 (2013) 3079–3093.
[99] P. Hydbring, M. Malumbres, P. Sicinski, Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases, Nat. Rev. Mol. Cell Biol. 17 (2016) 280.
[100] Y. Hong, J. Won, Y. Lee, S. Lee, K. Park, K.T. Chang, Y. Hong, Melatonin treatment induces interplay of apoptosis, autophagy, and senescence in human colorectal cancer cells, J. Pineal Res. 56 (2014) 264–274.
[101] G. Cini, B. Neri, A. Pacini, V. Cesati, C. Sassoli, S. Quattrone, M. D'apolito, A. Fazio, G. Scapagnini, A. Provenzani, Antiproliferative activity of melatonin by transcriptional inhibition of cyclin D1 expression: a molecular basis for melatonin-induced oncostatic effects, J. Pineal Res. 39 (2005) 12–20.
[102] O. Rögelsperger, K. Wlcek, C. Ekmekcioglu, S. Humpeler, M. Svoboda, R. Königsberg, M. Klimpfinger, W. Jäger, T. Thalhammer, Melatonin receptors, melatonin metabolizing enzymes and cyclin D1 in human breast cancer, J. Recept. Signal Transduct. 31 (2011) 180–187.
[103] S.W. Siu, K.W. Lau, P.C. Tam, S.Y. Shiu, Melatonin and prostate cancer cell proliferation: interplay with castration, epidermal growth factor, and androgen sensitivity, Prostate 52 (2002) 106–122.
[104] S.C. Xi, S.W. Siu, S.W. Fong, S.Y. Shiu, Inhibition of androgen-sensitive LNCaP prostate cancer growth in vivo by melatonin: association of antiproliferative action of the pineal hormone with mt1 receptor protein expression, Prostate 46 (2001) 52–61.
[105] H.Q. Ju, H. Li, T. Tian, Y.X. Lu, L. Bai, L.Z. Chen, H. Sheng, H.Y. Mo, J.B. Zeng, W. Deng, Melatonin overcomes gemcitabine resistance in pancreatic ductal adenocarcinoma by abrogating nuclear factor-κB activation, J. Pineal Res. 60 (2016) 27–38.
[106] M. Margheri, N. Pacini, A. Tani, D. Nosi, R. Squecco, A. Dama, E. Masala, F. Francini, S. Zecchi-Orlandini, L. Formigli, Combined effects of melatonin and all-trans retinoic acid and somatostatin on breast cancer cell proliferation and death: molecular basis for the anticancer effect of these molecules, Eur. J. Pharmacol. 681 (2012) 34–43.
[107] S. Carbajo-Pescador, J. Martín-Renedo, A. García-Palomo, M.J. Tuñón, J.L. Mauriz, J. González-Gallego, Changes in the expression of melatonin receptors induced by melatonin treatment in hepatocarcinoma HepG2 cells, J. Pineal Res. 47 (2009) 330–338.
[108] M. Mediavilla, S. Cos, E. Sanchez-Barcelo, Melatonin increases p53 and p21WAFl expression in MCF-7 human breast cancer cells in vitro, Life Sci. 65 (1999) 415–420.
[109] Y. Zhang, B. Chen, X. Wang, S. He, Effect of melatonin (MT) on proliferation of H22 cells and expression of p27-(Kip1) and cyclin Dl genes, Tumor 3 (2005), 008.
[110] O. Rögelsperger, Expression of Cell Cycle Regulators and Melatonin Receptor 1 in Human Breast Cancer Tissue, uniwien, 2009.
[111] C.W. Tam, K.W. Chan, V.W. Liu, B. Pang, K.M. Yao, S.Y. Shiu, Melatonin as a negative mitogenic hormonal regulator of human prostate epithelial cell growth: potential mechanisms and clinical significance, J. Pineal Res. 45 (2008) 403–412.
[112] S.Y. Shiu, W.Y. Leung, C.W. Tam, V.W. Liu, K.M. Yao, Melatonin MT1 receptor-induced transcriptional up-regulation of p27Kip1 in prostate cancer anti-proliferation is mediated via inhibition of constitutively active nuclear factor kappa B (NF-κB): potential implications on prostate cancer chemoprevention and therapy, J. Pineal Res. 54 (2013) 69–79.
[113] C. Tam, H. Mo, K. Yao, S. Shiu, Melatonin Inhibits the Proliferation of Hormone-Refractory Prostate Cancer Cells by Up-Regulating P27 Kip1 Expression and Down-Regulating Activated Androgen Signal Transduction via Membrane MT1 Receptor Activation, NCRI Cancer Conference, Birmingham, UK, 2006.
[114] S.S. Nah, H.J. Won, H.J. Park, E. Ha, J.H. Chung, H.Y. Cho, H.H. Baik, Melatonin inhibits human fibroblast-like synoviocyte proliferation via extracellular signal-regulated protein kinase/P21CIP1/P27KIP1 pathways, J. Pineal Res. 47 (2009) 70–74.
[115] I. Quiros, J.C. Mayo, O. Garcia-Suarez, D. Hevia, V. Martin, C. Rodríguez, R.M. Sainz, Melatonin prevents glucocorticoid inhibition of cell proliferation and toxicity in hippocampal cells by reducing glucocorticoid receptor nuclear translocation, J. Steroid Biochem. Mol. Biol. 110 (2008) 116–124.
[116] H. Jang, Y. Na, K. Hong, S. Lee, S. Moon, M. Cho, M. Park, O.H. Lee, E.M. Chang, D.R. Lee, Synergistic effect of melatonin and ghrelin in preventing cisplatin-induced ovarian damage via regulation of FOXO3a phosphorylation and binding to the p27Kip1 promoter in primordial follicles, J. Pineal Res. 3 (63) (2017) e12432.
[117] C.H. Kim, Y.-M. Yoo, Melatonin induces apoptotic cell death via p53 in LNCaP cells, KOREAN J. PHYSIOL. PHARMACOL. 14 (2010) 365–369.
[118] M.-h. She, C.-l. Huang, H.-y. Xie, Increasing of P53 in H22 hepatoma cells by melatonin, J. Nanhua Univ. (Med. Ed.) 6 (2008), 008.
[119] M. She, B. Chen, X. Wang, S. He, Mechanism of antiproliferation by melatonin on H22 cells, Chin. J. Histochem. Cytochem. 12 (2003) 383–387.
[120] Y. Hong, J. Won, K. Park, Melatonin is up-regulator on small G-protein mediated apoptotic cell death in cervical and endometrial cancer cells of human, Faseb. J. 23 (2009), 526.512-526.512.
[121] L. Xu, Q. Jin, X. Gong, H. Liu, R. Zhou, Anti-gastric cancer effect of melatonin and Bcl-2, Bax, p21 and p53 expression changes, Sheng li xue bao, Acta Physiol. Sin. 66 (2014) 723–729.
[122] R. Santoro, M. Marani, G. Blandino, P. Muti, S. Strano, Melatonin triggers p53Ser phosphorylation and prevents DNA damage accumulation, Oncogene 31 (2012) 2931.
[123] S.M. Mir, A. Aliarab, G. Goodarzi, M. Shirzad, S.M. Jafari, D. Qujeq, S. Samavarchi Tehrani, J. Asadi, Melatonin: A Smart Molecule in the DNA Repair System, Cell Biochemistry and Function, 2021.
[124] S. Proietti, A. Cucina, G. Dobrowolny, F. D'anselmi, S. Dinicola, M.G. Masiello, A. Pasqualato, A. Palombo, V. Morini, R.J. Reiter, Melatonin down-regulates MDM2 gene expression and enhances p53 acetylation in MCF-7 cells, J. Pineal Res. 57 (2014) 120–129.
[125] R. Santoro, F. Mori, M. Marani, G. Grasso, M.A. Cambria, G. Blandino, P. Muti, S. Strano, Blockage of melatonin receptors impairs p53-mediated prevention of DNA damage accumulation, Carcinogenesis 34 (2013) 1051–1061.
[126] I. Bejarano, P.C. Redondo, J. Espino, J.A. Rosado, S.D. Paredes, C. Barriga, R.J. Reiter, J.A. Pariente, A.B. Rodríguez, Melatonin induces mitochondrial-mediated apoptosis in human myeloid HL-60 cells, J. Pineal Res. 46 (2009) 392–400.
[127] O. Trubiani, R. Recchioni, F. Moroni, J. Pizzicannella, S. Caputi, R. Di Primio, Melatonin provokes cell death in human B-lymphoma cells by mitochondrial-dependent apoptotic pathway activation, J. Pineal Res. 39 (2005) 425–431.
[128] K. Kandasamy, S.M. Srinivasula, E.S. Alnemri, C.B. Thompson, S.J. Korsmeyer, J.L. Bryant, R.K. Srivastava, Involvement of proapoptotic molecules Bax and Bak in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced mitochondrial disruption and apoptosis, Cancer Res. 63 (2003) 1712–1721.
[129] S. Rubio, F. Estévez, J. Cabrera, R.J. Reiter, J. Loro, J. Quintana, Inhibition of proliferation and induction of apoptosis by melatonin in human myeloid HL-60 cells, J. Pineal Res. 42 (2007) 131–138.
[130] J. Wang, X. Xiao, Y. Zhang, D. Shi, W. Chen, L. Fu, L. Liu, F. Xie, T. Kang, W. Huang, Simultaneous modulation of COX-2, p300, Akt, and Apaf-1 signaling by melatonin to inhibit proliferation and induce apoptosis in breast cancer cells, J. Pineal Res. 53 (2012) 77–90.
[131] S.B. Bratton, G. Walker, S.M. Srinivasula, X.M. Sun, M. Butterworth, E.S. Alnemri, G.M. Cohen, Recruitment, activation and retention of caspases-9 and-3 by Apaf-1 apoptosome and associated XIAP complexes, EMBO J. 20 (2001) 998–1009.
[132] S.S. Joo, Y.M. Yoo, Melatonin induces apoptotic death in LNCaP cells via p38 and JNK pathways: therapeutic implications for prostate cancer, J. Pineal Res.

47 (2009) 8–14.
[133] Q. Lu, P. Sakhatskyy, J. Newton, P. Shamirian, V. Hsiao, S. Curren, G.A.G. Miranda, M. Pedroza, M.R. Blackburn, S. Rounds, Sustained adenosine exposure causes lung endothelial apoptosis: a possible contributor to cigarette smoke-induced endothelial apoptosis and lung injury, Am. J. Physiol. Lung Cell Mol. Physiol. 304 (2013) L361–L370.
[134] H.-J. Lee, C.-J. Wang, H.-C. Kuo, F.-P. Chou, L.-F. Jean, T.-H. Tseng, Induction apoptosis of luteolin in human hepatoma HepG2 cells involving mitochondria translocation of Bax/Bak and activation of JNK, Toxicol. Appl. Pharmacol. 203 (2005) 124–131.
[135] S. Carbajo-Pescador, C. Steinmetz, A. Kashyap, S. Lorenz, J. Mauriz, M. Heise, P. Galle, J. Gonzalez-Gallego, S. Strand, Melatonin induces transcriptional regulation of Bim by FoxO3a in HepG2 cells, Br. J. Cancer 108 (2013) 442.
[136] S.M. Mir, B. Yousefi, A. Marjani, M. Rahimi, D. Qujeq, The sensitization of melatonin in osteosarcoma cells by suppression of anti-apoptotic proteins, Pharmaceut. Sci. 26 (2020) 159–164.
[137] G. Niu, B. Yousefi, D. Qujeq, A. Marjani, J. Asadi, Z. Wang, S.M. Mir, Melatonin and doxorubicin co-delivered via a functionalized graphene-dendrimeric system enhances apoptosis of osteosarcoma cells, Mater. Sci. Eng. C 119 (2021), 111554.
[138] M.A. Oskoii, N. Khatami, M. Majidinia, M.-A. Rezazadeh, S.M. Mir, A. Sadeghpour, B. Yousefi, Serum level of melatonin in patients with osteoarthritis and its relation with 8-hydroxy-2-deoxyguanosine and vitamin D, J. Res. Clin. Med. 8 (2020), 34-34.
[139] L. Fan, G. Sun, T. Ma, F. Zhong, W. Wei, Melatonin overcomes apoptosis resistance in human hepatocellular carcinoma by targeting survivin and XIAP, J. Pineal Res. 55 (2013) 174–183.
[140] W. Li, Z. Wang, Y. Chen, K. Wang, T. Lu, F. Ying, M. Fan, Z. Li, J. Wu, Melatonin treatment induces apoptosis through regulating the nuclear factor-κB and mitogen-activated protein kinase signaling pathways in human gastric cancer SGC7901 cells, Oncol. Lett. 13 (2017) 2737.
[141] J.Y. Wei, W.M. Li, L.L. Zhou, Q.N. Lu, W. He, Melatonin induces apoptosis of colorectal cancer cells through HDAC4 nuclear import mediated by CaMKII inactivation, J. Pineal Res. 58 (2015) 429–438.
[142] H.J. Um, J.H. Oh, Y.-N. Kim, Y.H. Choi, S.H. Kim, J.-W. Park, T.K. Kwon, The coffee diterpene kahweol sensitizes TRAIL-induced apoptosis in renal carcinoma Caki cells through down-regulation of Bcl-2 and c-FLIP, Chem. Biol. Interact. 186 (2010) 36–42.
[143] Y. Gao, X. Xiao, C. Zhang, W. Yu, W. Guo, Z. Zhang, Z. Li, X. Feng, J. Hao, K. Zhang, Melatonin synergizes the chemotherapeutic effect of 5-fluorouracil in colon cancer by suppressing PI3K/AKT and NF-κB/iNOS signaling pathways, J. Pineal Res. 2 (62) (2016) e12380.
[144] S.M. Mir, S.S. Tehrani, G. Goodarzi, Z. Jamalpoor, J. Asadi, N. Khelghati, D. Qujeq, M. Maniati, Shelterin complex at telomeres: implications in ageing, Clin. Interv. Aging 15 (2020) 827.
[145] K. Singletary, J. Milner, Diet, autophagy, and cancer: a review, Cancer Epidemiol. Prev. Biomark. 17 (2008) 1596–1610.
[146] C. He, D.J. Klionsky, Regulation mechanisms and signaling pathways of autophagy, Annu. Rev. Genet. 43 (2009) 67–93.
[147] J. Yu, A. Parkhitko, E.P. Henske, Autophagy, Autophagy, 2011.
[148] J. Kim, M. Kundu, B. Viollet, K.-L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2011) 132.
[149] J. Wu, Y. Bai, Y. Wang, J. Ma, Melatonin and regulation of autophagy: mechanisms and therapeutic implications, Pharmacol. Res. 163 (2021), 105279.
[150] N. Mizushima, The role of the Atg1/ULK1 complex in autophagy regulation, Curr. Opin. Cell Biol. 22 (2010) 132–139.
[151] S.I. Choi, K.S. Kim, J.Y. Oh, J.Y. Jin, G.H. Lee, E.K. Kim, Melatonin induces autophagy via an mTOR-dependent pathway and enhances clearance of mutant-TGFBIp, J. Pineal Res. 54 (2013) 361–372.
[152] C.C. Chang, T.Y. Huang, H.Y. Chen, T.C. Huang, L.C. Lin, Y.J. Chang, S.M. Hsia, Protective Effect of Melatonin against Oxidative Stress-Induced Apoptosis and Enhanced Autophagy in Human Retinal Pigment Epithelium Cells, Oxidative Medicine and Cellular Longevity, vol. 2018, 2018, p. 9015765.
[153] S.J. Cherra, S.M. Kulich, G. Uechi, M. Balasubramani, J. Mountzouris, B.W. Day, C.T. Chu, Regulation of the autophagy protein LC3 by phosphorylation, J. Cell Biol. 190 (2010) 533–539.
[154] K. Matsunaga, T. Saitoh, K. Tabata, H. Omori, T. Satoh, N. Kurotori, I. Maejima, K. Shirahama-Noda, T. Ichimura, T. Isobe, Two Beclin 1-binding proteins, Atg14L and Rubicon, reciprocally regulate autophagy at different stages, Nat. Cell Biol. 11 (2009) 385.
[155] R. Kang, H. Zeh, M. Lotze, D. Tang, The Beclin 1 network regulates autophagy and apoptosis, Cell Death Differ. 18 (2011) 571.
[156] K. Ding, J. Xu, H. Wang, L. Zhang, Y. Wu, T. Li, Melatonin protects the brain from apoptosis by enhancement of autophagy after traumatic brain injury in mice, Neurochem. Int. 91 (2015) 46–54.
[157] T. Ali, S.U. Rahman, Q. Hao, W. Li, Z. Liu, F. Ali Shah, I. Murtaza, Z. Zhang, X. Yang, G. Liu, S. Li, Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation, J. Pineal Res. 69 (2020), e12667.
[158] S. Joshi, L.-C. Pantalena, X.K. Liu, S.L. Gaffen, H. Liu, C. Rohowsky-Kochan, K. Ichiyama, A. Yoshimura, L. Steinman, S. Christakos, S. Youssef, 1,25-dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A, Mol. Cell Biol. 31 (2011) 3653–3669.
[159] D. Liu, Z. Ma, S. Di, Y. Yang, J. Yang, L. Xu, R.J. Reiter, S. Qiao, J. Yuan, AMPK/PGC1α activation by melatonin attenuates acute doxorubicin cardiotoxicity via alleviating mitochondrial oxidative damage and apoptosis, Free Radic. Biol. Med. 129 (2018) 59–72.
[160] P. Sharma, H. Sampath, Mitochondrial DNA integrity: role in health and disease, Cells 8 (2019) 100.
[161] R.J. Reiter, D.X. Tan, S. Rosales-Corral, A. Galano, M.-J. Jou, D. Acuna-Castroviejo, Melatonin mitigates mitochondrial meltdown: interactions with SIRT3, Int. J. Mol. Sci. 19 (2018) 2439.
[162] L. Liu, Q. Cao, W. Gao, B. Li, Z. Xia, B. Zhao, Melatonin protects against focal cerebral ischemia-reperfusion injury in diabetic mice by ameliorating mitochondrial impairments: involvement of the Akt-SIRT3-SOD2 signaling pathway, Aging (Albany NY) 13 (2021) 16105.
[163] Z. Fang, K.H. Jung, H.H. Yan, S.-J. Kim, M. Rumman, J.H. Park, B. Han, J.E. Lee, Y. wool Kang, J.H. Lim, Melatonin synergizes with sorafenib to suppress pancreatic cancer via melatonin receptor and PDGFR-β/STAT3 pathway, Cell. Physiol. Biochem. 47 (2018) 1751–1768.
[164] M. Yang, L. Li, S. Chen, S. Li, B. Wang, C. Zhang, Y. Chen, L. Yang, H. Xin, C. Chen, Melatonin protects against apoptosis of megakaryocytic cells via its receptors and the AKT/mitochondrial/caspase pathway, Aging (Albany NY) 12 (2020) 13633.
[165] A. Cutando, A. Lopez-Valverde, S. Arias-Santiago, J. De Vicente, R.G. De Diego, Role of melatonin in cancer treatment, Anticancer Res. 32 (2012) 2747–2753.
[166] C. Dong, L. Yuan, J. Dai, L. Lai, L. Mao, S. Xiang, B. Rowan, S.M. Hill, Melatonin inhibits mitogenic cross-talk between retinoic acid-related orphan receptor alpha (RORα) and ERα in MCF-7 human breast cancer cells, Steroids 75 (2010) 944–951.
[167] G. Meıen-Mucha, K. Winczyk, M. Pawlikowski, Somatostatin analogue octreotide and melatonin inhibit bromodeoxyuridine incorporation into cell nuclei and enhance apoptosis in the transplantable murine colon 38 cancer, Anticancer Res. 18 (1997) 3615–3619.
[168] P. Lissoni, F. Paolorossi, G. Tancini, A. Ardizzoia, S. Barni, F. Brivio, G. Maestroni, M. Chilelli, A phase II study of tamoxifen plus melatonin in metastatic solid tumour patients, Br. J. Cancer 74 (1996) 1466.
[169] M. Akbarzadeh, A.A. Movassaghpour, H. Ghanbari, M. Kheirandish, N. Fathi Maroufi, R. Rahbarghazi, M. Nouri, N. Samadi, The potential therapeutic effect of melatonin on human ovarian cancer by inhibition of invasion and migration of cancer stem cells, Sci. Rep. 7 (2017) 17062.
[170] A. Conti, G.J. Maestroni, The clinical neuroimmunotherapeutic role of melatonin in oncology, J. Pineal Res. 19 (1995) 103–110.
[171] P. Lissoni, M. Chilelli, S. Villa, L. Cerizza, G. Tancini, Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial, J. Pineal Res. 35 (2003) 12–15.
[172] M. Emet, H. Ozcan, L. Ozel, M. Yayla, Z. Halici, A. Hacimuftuoglu, A review of melatonin, its receptors and drugs, Eurasian J. Med. 48 (2016) 135–141.
[173] G. Tosini, S. Owino, J.L. Guillaume, R. Jockers, Understanding melatonin receptor pharmacology: latest insights from mouse models, and their relevance to human disease, Bioessays : news and reviews in molecular, cellular and developmental biology 36 (2014) 778–787.
[174] C. Ekmekcioglu, T. Thalhammer, S. Humpeler, M.R. Mehrabi, H.D. Glogar, T. Hölzenbein, O. Markovic, V.J. Leibetseder, G. Strauss-Blasche, W. Marktl, The melatonin receptor subtype MT2 is present in the human cardiovascular system, J. Pineal Res. 35 (2003) 40–44.
[175] Y.Q. Wang, Y.J. Jiang, M.S. Zou, J. Liu, H.Q. Zhao, Y.H. Wang, Antidepressant actions of melatonin and melatonin receptor agonist: focus on pathophysiology and treatment, Behav. Brain Res. 420 (2022), 113724.
[176] K. Winczyk, M. Pawlikowski, J.M. Guerrero, M. Karasek, Possible involvement of the nuclear RZR/ROR-alpha receptor in the antitumor action of melatonin on murine Colon 38 cancer, Tumour Biol. : the journal of the International Society for Oncodevelopmental Biology and Medicine 23 (2002) 298–302.
[177] A. Cutando, J. Aneiros-Fernández, A. López-Valverde, S. Arias-Santiago, J. Aneiros-Cachaza, R.J. Reiter, A new perspective in Oral health: potential importance and actions of melatonin receptors MT1, MT2, MT3, and RZR/ROR in the oral cavity, Arch. Oral Biol. 56 (2011) 944–950.
[178] P. Plaimee, N. Weerapreeyakul, S. Barusrux, N. Johns, Melatonin potentiates cisplatin-induced apoptosis and cell cycle arrest in human lung adenocarcinoma cells, Cell Prolif 48 (2015) 67–77.
[179] S. Casado-Zapico, J. Rodriguez-Blanco, G. García-Santos, V. Martín, A.M. Sánchez-Sánchez, I. Antolín, C. Rodriguez, Synergistic antitumor effect of melatonin with several chemotherapeutic drugs on human Ewing sarcoma cancer cells: potentiation of the extrinsic apoptotic pathway, J. Pineal Res. 48 (2010) 72–80.
[180] J.H. Kim, S.J. Jeong, B. Kim, S.M. Yun, D.Y. Choi, S.H. Kim, Melatonin synergistically enhances cisplatin-induced apoptosis via the dephosphorylation of ERK/p90 ribosomal S6 kinase/heat shock protein 27 in SK-OV-3 cells, J. Pineal Res. 52 (2012) 244–252.
[181] L.-L. Fan, G.-P. Sun, W. Wei, Z.-G. Wang, L. Ge, W.-Z. Fu, H. Wang, Melatonin and doxorubicin synergistically induce cell apoptosis in human hepatoma cell lines, World J. Gastroenterol.: WJG 16 (2010) 1473.
[182] A.C. Uguz, B. Cig, J. Espino, I. Bejarano, M. Naziroglu, A.B. Rodríguez, J.A. Pariente, Melatonin potentiates chemotherapy-induced cytotoxicity and apoptosis in rat pancreatic tumor cells, J. Pineal Res. 53 (2012) 91–98.
[183] A. Rodriguez-Garcia, J.C. Mayo, D. Hevia, I. Quiros-Gonzalez, M. Navarro, R.M. Sainz, Phenotypic changes caused by melatonin increased sensitivity of

prostate cancer cells to cytokine-induced apoptosis, J. Pineal Res. 54 (2013) 33–45.
[184] L. Fan, G. Sun, T. Ma, F. Zhong, Y. Lei, X. Li, W. Wei, Melatonin reverses tunicamycin-induced endoplasmic reticulum stress in human hepatocellular carcinoma cells and improves cytotoxic response to doxorubicin by increasing CHOP and decreasing Survivin, J. Pineal Res. 55 (2013) 184–194.
[185] V. Martín, G. García-Santos, J. Rodriguez-Blanco, S. Casado-Zapico, A. Sanchez-Sanchez, I. Antolín, M. Medina, C. Rodriguez, Melatonin sensitizes human malignant glioma cells against TRAIL-induced cell death, Cancer Lett. 287 (2010) 216–223.
[186] R. Pariente, J.A. Pariente, A.B. Rodríguez, J. Espino, Melatonin sensitizes human cervical cancer HeLa cells to cisplatin-induced cytotoxicity and apoptosis: effects on oxidative stress and DNA fragmentation, J. Pineal Res. 60 (2016) 55–64.
[187] L. Zha, L. Fan, G. Sun, H. Wang, T. Ma, F. Zhong, W. Wei, Melatonin sensitizes human hepatoma cells to endoplasmic reticulum stress–induced apoptosis, J. Pineal Res. 52 (2012) 322–331.
[188] S.M. Woo, K.j. Min, T.K. Kwon, Melatonin-mediated Bim up-regulation and cyclooxygenase-2 (COX-2) down-regulation enhances tunicamycin-induced apoptosis in MDA-MB-231 cells, J. Pineal Res. 58 (2015) 310–320.
[189] W. Koh, S.J. Jeong, H.J. Lee, H.G. Ryu, E.O. Lee, K.S. Ahn, H. Bae, S.H. Kim, Melatonin promotes puromycin-induced apoptosis with activation of caspase-3 and 5′-adenosine monophosphate-activated kinase-alpha in human leukemia HL-60 cells, J. Pineal Res. 50 (2011) 367–373.
[190] N. Prieto-Domínguez, R. Ordóñez, A. Fernández, C. Méndez-Blanco, A. Baulies, C. Garcia-Ruiz, J.C. Fernández-Checa, J.L. Mauriz, J. González-Gallego, Melatonin-induced increase in sensitivity of human hepatocellular carcinoma cells to sorafenib is associated with reactive oxygen species production and mitophagy, J. Pineal Res. 61 (2016) 396–407.
[191] Y. Gao, X. Xiao, C. Zhang, W. Yu, W. Guo, Z. Zhang, Z. Li, X. Feng, J. Hao, K. Zhang, Melatonin synergizes the chemotherapeutic effect of 5-fluorouracil in colon cancer by suppressing PI3K/AKT and NF-κB/iNOS signaling pathways, J. Pineal Res. (2017) 62.
[192] M. Fic, M. Podhorska-Okolow, P. Dziegiel, E. Gebarowska, T. Wysocka, M. Drag-Zalesinska, M. Zabel, Effect of melatonin on cytotoxicity of doxorubicin toward selected cell lines (human keratinocytes, lung cancer cell line A-549, laryngeal cancer cell line Hep-2), in: Vivo, vol. 21, 2007, pp. 513–518.
[193] P.A. Koşar, M. Nazıroğlu, İ.S. Övey, B. Çiğ, Synergic effects of doxorubicin and melatonin on apoptosis and mitochondrial oxidative stress in MCF-7 breast cancer cells: involvement of TRPV1 channels, J. Membr. Biol. 249 (2016) 129–140.
[194] U. Wenzel, A. Nickel, H. Daniel, Melatonin potentiates flavone-induced apoptosis in human colon cancer cells by increasing the level of glycolytic end products, Int. J. Cancer 116 (2005) 236–242.
[195] I. Bejarano, J. Espino, A.M. Marchena, C. Barriga, S.D. Paredes, A.B. Rodríguez, J.A. Pariente, Melatonin enhances hydrogen peroxide-induced apoptosis in human promyelocytic leukaemia HL-60 cells, Mol. Cell. Biochem. 353 (2011) 167.
[196] S. Proietti, A. Cucina, F. D'Anselmi, S. Dinicola, A. Pasqualato, E. Lisi, M. Bizzarri, Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFβ-1-dependent growth inhibition of breast cancer cells, J. Pineal Res. 50 (2011) 150–158.
[197] S.-M. Yun, S.H. Woo, S.T. Oh, S.-E. Hong, T.-B. Choe, S.-K. Ye, E.-K. Kim, M.K. Seong, H.-A. Kim, W.C. Noh, Melatonin enhances arsenic trioxide-induced cell death via sustained upregulation of Redd1 expression in breast cancer cells, Mol. Cell. Endocrinol. 422 (2016) 64–73.
[198] W. Li, M. Fan, Y. Chen, Q. Zhao, C. Song, Y. Yan, Y. Jin, Z. Huang, C. Lin, J. Wu, Melatonin induces cell apoptosis in AGS cells through the activation of JNK and P38 MAPK and the suppression of nuclear factor-kappa B: a novel therapeutic implication for gastric cancer, Cell. Physiol. Biochem. 37 (2015) 2323–2338.
[199] L.G.A. Chuffa, M.S. Alves, M. Martinez, I.C.C. Camargo, P.F. Pinheiro, R.F. Domeniconi, L.A.L. Júnior, F.E. Martinez, Apoptosis is triggered by melatonin in an in vivo model of ovarian carcinoma, Endocr. Relat. Cancer 23 (2016) 65–76.
[200] A. Cucina, S. Proietti, F. D'Anselmi, P. Coluccia, S. Dinicola, L. Frati, M. Bizzarri, Evidence for a biphasic apoptotic pathway induced by melatonin in MCF-7 breast cancer cells, J. Pineal Res. 46 (2009) 172–180.
[201] C. Fan, Y. Pan, Y. Yang, S. Di, S. Jiang, Z. Ma, T. Li, Z. Zhang, W. Li, X. Li, HDAC1 inhibition by melatonin leads to suppression of lung adenocarcinoma cells via induction of oxidative stress and activation of apoptotic pathways, J. Pineal Res. 59 (2015) 321–333.
[202] G. García-Santos, I. Antolín, F. Herrera, V. Martín, J. Rodriguez-Blanco, M.d.P. Carrera, C. Rodriguez, Melatonin induces apoptosis in human neuroblastoma cancer cells, J. Pineal Res. 41 (2006) 130–135.
[203] A. Leja-Szpak, J. Jaworek, P. Pierzchalski, R.J. Reiter, Melatonin induces pro-apoptotic signaling pathway in human pancreatic carcinoma cells (PANC-1), J. Pineal Res. 49 (2010) 248–255.
[204] U. Laothong, Y. Hiraku, S. Oikawa, K. Intuyod, M. Murata, S. Pinlaor, Melatonin induces apoptosis in cholangiocarcinoma cell lines by activating the reactive oxygen species-mediated mitochondrial pathway, Oncol. Rep. 33 (2015) 1443–1449.
[205] P. Plaimee, N. Weerapreeyakul, K. Thumanu, W. Tanthanuch, S. Barusrux, Melatonin induces apoptosis through biomolecular changes, in: SK-LU-1 Human Lung Adenocarcinoma Cells, Cell Proliferation, vol. 47, 2014, pp. 564–577.
[206] M. Sánchez-Hidalgo, M. Lee, C.A. de la Lastra, J.M. Guerrero, G. Packham, Melatonin inhibits cell proliferation and induces caspase activation and apoptosis in human malignant lymphoid cell lines, J. Pineal Res. 53 (2012) 366–373.
[207] S. Zhang, Y. Qi, H. Zhang, W. He, Q. Zhou, S. Gui, Y. Wang, Melatonin inhibits cell growth and migration, but promotes apoptosis in gastric cancer cell line, SGC7901, Biotech. Histochem. 88 (2013) 281–289.