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THE PRO-APOPTOTIC MECHANISMS OF MELATONIN IN CANCER

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Abstract

Cancer is a leading cause of morbidity and mortality worldwide. Various therapies including chemotherapy, radiation therapy, surgery and hormone therapy have been used in the past decades to treat cancers. However, most treatments are associated with unwanted side effects; therefore a better anticancer approach that has less severe side effects and better efficacy is needed. Melatonin is an endogenous indolamine hormone that is mainly produced and secreted by pineal gland. It has oncostatic properties and induces apoptosis in cancer cells. This review describes the pro-apoptotic mechanisms of melatonin on a variety of tumor cells.

INTRODUCTION

Cancer has been a leading cause of morbidity and mortality worldwide and has been presented as a common public health problem in many countries. World Health Organization (WHO) has reported that there were approximately 14.1 million cancer patients around the world in 2012. Globally, nearly 8.8 million cases of cancer deaths occurred in 2015, of which one in every six people died from cancer [1]. Various therapies including bone marrow and stem cell transplantation, radiation therapy, chemotherapy and surgery have been used in the past decades to treat cancers. On top of that, hormone therapy, immunotherapy and targeted therapy are also available to treat cancers. However, the choice of cancer treatment is largely dependent on the type and size of tumors, the extent of metastasis, the specific molecular characteristics of cancer cells and the patient preferences [2].

At present, the advances in surgical techniques and combined therapies succeed in providing positive outcomes to patients. Although there have been improvements of five-years relative survival rates in the majority of cancers, several studies have indicated that the survival rates for certain cancers such as pancreatic cancer, lung cancer and brain cancer still remain at low percentages [3]. Apart from that, most treatments are invasive and associated with unwanted side effects such as emotional distress, pain, anxiety, fatigue, loss of bone density, neurotoxicity, cardio-toxicity, infertility [4-6]. Therefore, a better anticancer approach that has less severe side effects and better efficacy is needed to improve the cancer patients' quality of life.

Melatonin, or N-acetyl-5-methoxytryptamine, which derived from amino acid L-tryptophan via serotonin, is an endogenous indolamine hormone that is mainly produced and secreted by pineal gland. It is also synthesized in several extra-pineal tissues such as gastrointestinal tract, kidneys, skin, bone marrow, lymphocytes and retina [7]. Subsequently, this indoleamine plays multiple important roles in physiological functions including regulatory control of circadian rhythms, mood, sleep, aging disease, anti-inflammation, anti-oxidative processes and immunomodulation [8-10]. In addition, melatonin confers oncostatic properties via inhibition of cancer cell metastasis, suppresses tumor growth, promotes apoptosis, inhibits telomerase activity and angiogenesis, reduces carcinogenesis as well as induces cell cycle arrest [11, 12].

Previous evidence has suggested that melatonin is anti-apoptotic in normal cells but pro-apoptotic in cancer cells [12]. Meanwhile, there were studies carried out in *in vitro* experimental models of neoplasia to prove that melatonin can uniformly provoke cytotoxic effect in tumor cells through modulation of multiple signaling pathways. The present review focused on the molecular insights into the mechanisms involved in pro-apoptotic effect of melatonin on a variety of tumor cells.

MECHANISMS OF ACTION INVOLVED IN THE PRO-APOPTOTIC EFFECT OF MELATONIN

Regulation of cell proliferation

Melatonin is known to induce anti-proliferative effects in different types of cancer cell lines that summarized in **Table 1** [13-23]. The inhibition of cell proliferation is dose and time-dependent, with markedly accumulation of cell numbers in sub-G_1 phase of cell cycle or induction of G_2/M arrest [15-18, 21, 23]. As such, the increased number of cells with hypodiploid DNA content in sub-G_1 phase indicated that apoptotic cell deaths were occurred in cancer cell lines whereas the cell cycle arrest in G_2/M is associated with inhibition of cell proliferation [12]. Additionally, several studies also indicated that melatonin-induced sub-G_1 and G_2/M phase arrest of cancer cell lines are associated with decreased activities of p21 proteins [13], repressed phosphorylation of ERK and the transcriptional downregulation of cyclin-dependent kinases expression including cyclin B1, cyclin D1, CDK4 and CDK1 [14, 15], thereby promoting cell cycle arrest and inhibits the proliferation of cancer cell.

Table 1. The effects of melatonin on cell cycle regulation

Tumor model	Mechanism(s) of action	Ref.
MCF-7 and T47D human breast cancer cells	Inhibited bisphenol A-induced breast cancer cell proliferation	[16]
MDA-MB-231 human breast cancer cells	Attenuated the expression of cyclin D1 and cyclin E	[15]
MDA-MB-361 human breast cancer cells	Increased the apoptotic sub-G_1 cell population Inhibited the expression of COX-2 Reduced prostaglandin E2 production	[17]
SGC-7901 human gastric cancer cells	Inhibited cell proliferation Arrested SGC-7901 cells in the G_1/S phase of cell cycle Reduced the expression of cell division cycle 25A (CDC25A), phospho-CDC25A (at Ser75), p21 (p21Cip1/p21Waf) and phospho-p21 (at Thr145)	[13]
HCT116 human colorectal adenocarcinoma cells	Induced G_1 phase arrest Decreased S phase population Attenuated E- and A-type cyclins	[14]
Molt-3 human lymphoid cells	Increased in the number of hypodiploid cells in sub-G_1 phase	[18]
A549 and PC9 human lung adenocarcinoma cells	Downregulated the proliferating cell nuclear antigen	[19]
OVCAR3 and SKOV3 ovarian cancer cells	Inhibited estrogen receptor α expression	[20]
OVCAR-429 and PA-1 ovarian cancer cells	Downregulated cyclin-dependent kinase (CDK) 2 and CDK 4 gene expression Induced cell cycle arrest at G_1 phase Decreased number of cells in S phase Increased G_2/M and sub-G_1 phase population	[21]
AsPc-1 and MiaPaCa-2 human pancreatic ductal adenocarcinoma cells	Decreased expression of cyclin D1	[22]
Caki human renal cancer cells	Increased in sub-G_1 population	[23]

Extrinsic death receptor pathway

Apoptotic cell death may be triggered by melatonin via induction of cysteine proteases family, known as caspases, which commit tumor cells to two pathways of apoptosis, including extrinsic and intrinsic pathways. Extrinsic pathway is initiated after extracellular death ligands bind to the cell surface death receptors, which are members of tumor necrosis factor (TNF) receptor superfamily including TNF-related apoptosis inducing ligand (TRAIL) receptors, CD95 (Fas) and TNF [24]. There was also evidence showing that melatonin induced the extrinsic pathway of apoptotic cell death in Ewing's sarcoma SK-N-MC cells by increasing the ligand Fas L expression and activating its Fas receptor as well as activating caspase-8 activity [25]. The death receptor then attracts cysteine proteases and adaptor proteins such as Fas-associated death domain (FADD) to form the multi-protein death-inducing signal complex (DISC). Subsequently, DISC activates procaspase-8 to initiator caspase-8, which eventually propagates apoptosis signaling though activation of executioner caspases. The activated caspase-3 cleaves the protein kinases, DNA repair proteins, inhibitory subunits of endonucleases family as well as inhibitor of caspase-activated deoxyribonuclease (CAD) to cause morphological changes of cancer cells [26].

Intrinsic mitochondrial pathway

In the pathway of intrinsic apoptosis, melatonin is capable of increasing mitochondrial outer membrane permeabilization and losing the mitochondrial transmembrane potential in cancer cells. Mitochondria are the central mediators of intrinsic pathway whereby its permeability can be increased to release cytochrome c and other pro-apoptotic factors including endonuclease G, second mitochondria-derived activator of caspases (Smac/DIABLO) and apoptosis-inducing factor (AIF) from mitochondrial intermembrane space into the cytoplasm. Cytochrome c will then promote the oligomerization of apoptotic protease-activating factor 1 (Apaf-1) and activate caspase-9 to develop apoptosome, leading to the activation of caspase-3 that can induce nuclear fragmentation, membrane blebbing, cell shrinkage and chromatin condensation of tumor cells [24, 26]. The pro-apoptotic effects of melatonin on intrinsic mitochondrial pathway are summarized in **Table 2**.

Table 2. The effects of melatonin on intrinsic mitochondrial pathway

Tumor model	Mechanism(s) of action	Ref.
KKU-M055 and KKU-M214 human cholangiocarcinoma cells	Enhanced production of cytochrome c Increased expression of caspase-3 and -7	[27]
MDA-MB-361 human breast cancer cells	Induced Apaf-1 expression Triggered the release of cytochrome c Stimulated caspase-3 and -9 activities Activated Apaf-1-dependent apoptotic pathway	[17]
SGC-7901 human gastric cancer cells	Increased caspase-3 activity and cleaved caspase-9 levels	[13]
SGC-7901 human gastric cancer cells	Activated caspase-3 activity	[28]
LoVo human colorectal cancer cells	Activated caspase-3 activity	[29]
HCT116 human colorectal adenocarcinoma cells	Led to cleavage of caspase-3	[14]
Molt-3 human lymphoid cells	Activated caspase-3, -6, -7 and -9 but not caspase-8 and -2 Upregulated the release of cytochrome c from mitochondria	[18]
A549 and PC9 human lung adenocarcinoma cells	Increased in the apoptotic index Increased caspase-3 activity	[19]
SK-LU-1 human lung adenocarcinoma cisplatin-sensitive cells	Activated caspase-3/7 Caused DNA fragmentation	[30]
MiaPACA-2 human pancreatic carcinoma cells	Increased cleavage of caspase-3	[31]
Caki human renal cancer cells	Upregulated the activation of caspase-3 and DNA fragmentation	[23]
RD and RH30 soft tissue sarcomas, rhabdomyosarcoma	Increased the levels of caspase-3 cleaved fragments	[32]
KTC-1 and BCPAP human papillary thyroid cancer cells, 8505c and ARO human anaplastic thyroid cancer cells	Increased caspase-3/7, cleavage of poly(ADP-ribose) polymerase (PARP), caspase-9 and cytochrome c expression	[33]

B-cell lymphoma (Bcl)-2 family proteins

In addition to caspase activation, melatonin can trigger apoptosis through the modification of anti-apoptotic and pro-apoptotic Bcl-2 family proteins. The pro-apoptotic Bcl-2 family proteins such as Bcl2-associated protein X (Bax), Bcl2-interacting mediator of cell death (Bim), Bcl2 antagonist/killer (Bak), BH3-interacting domain death agonist (Bid) and p53 upregulated modulator of apoptosis (Puma) are responsible to release apoptogenic factors by inducing the permeability of outer mitochondria membrane as well as function to neutralize the anti-apoptotic proteins [21]. In contrast, the anti-apoptotic proteins include B cell lymphoma extra-large (BcL-X_L), Bcl2-like 2 (Bcl-W), Bcl2-like 10 (Bcl-B), Bcl-2, myeloid leukemia cell differentiation protein (Mcl-1) and Bcl2-related protein A1 (Bfl-1) can maintain the membrane integrity and suppress the mitochondrial permeability transition pore to prevent cytochrome c release from mitochondria [26].

Several *in vitro* studies (**Table 3**) reported that melatonin can significantly upregulate and downregulate the expression of Bax as well as Bcl-2 respectively in tumor models to induce cellular apoptosis. Furthermore, the studies on the mode of action of melatonin revealed that melatonin can activate Bid, causing its translocation to mitochondria as truncated fragment of Bid (tBid) prior to the binding to the membrane-bound Bax. Then, Bax will oligomerize and promote membrane permeabilization of mitochondria to trigger a cascade of caspase activations which resulting in cellular apoptosis [34]. However, the molecular mechanisms of interaction between both tBid and Bax with mitochondrial membrane permeabilization still remain contentious.

Table 3. The effects of melatonin on BCL-2 family protein

Tumor model	Mechanism(s) of action	Ref.
MDA-MB-231 human breast cancer cells	Attenuated the expression of Bcl-xL and McL	[15]
SGC-7901 human gastric cancer cells	Upregulated Bax protein expression Downregulated Bcl-xL protein expression	[13]
Gastric cancer cells	Increased Bax protein expression Decreased Bcl-2 protein expression	[35]
LoVo human colorectal cancer cells	Reduced H3 acetylation on Bcl-2 promoter, leading to suppression of Bcl-2 expression Induced dephosphorylation and nuclear import of histone deacetylase 4 (HDAC4) Inhibited CaMKIIα phosphorylation	[29]
HCT116 human colorectal adenocarcinoma cells	Upregulated Bax and Bcl-xL	[14]
SK-N-MC Ewing's sarcoma cells	Increased the expression of Bcl-Xs	[25]
HepG2 human hepatoma cells	Decreased Bcl-2/Bax ratio	[36]
HepG2 human hepatoblastoma cells	Increased the expression of BH2-only protein Bim	[37]
Molt-3 human lymphoid cells	Upregulated Bax	[18]
A549 and PC9 human lung adenocarcinoma cells	Upregulated PUMA and Bax Downregulated Bcl-2	[19]
SOSP-9607 human osteosarcoma cell line	Upregulated Bax and cytochrome c Downregulated Bcl-2	[38]
MiaPACA-2 human pancreatic carcinoma cells	Increased Bax protein expression Decreased Bcl-2 protein expression	[31]
AsPc-1 and MiaPaCa-2 human pancreatic ductal adenocarcinoma cells	Downregulated the expression of Bcl-xL	[22]
SW-1990 pancreatic cancer	Downregulated Bcl-2 expression Upregulated Bax expression	[39]

cells		
Caki human renal cancer cells	Upregulated Bim at transcriptional and post-transcriptional level Did not alter Bax, Bcl-2, Mcl-1 and Bcl-xL	[23]
RD and RH30 soft tissue sarcomas, rhabdomyosarcoma	Increased Bax expression Downregulated Bcl-2 expression	[32]

Mitogen-activated protein kinases (MAPK) pathway

The MAPK superfamily mainly consists of three members, including p38 MAPK, c-JUN N-terminal kinase/stress-activated protein kinase (JNK/SAPK) and extracellular signal-regulated kinase (ERK). They are serine and threonine kinases that transduce external signals from cell membrane to the nucleus for wide range of cellular processes. The MAPK signaling transduction pathway controls gene expression as well as cell proliferation, differentiation and apoptosis. JNK and p38 MAPK are simultaneously activated by environmental and intracellular stresses such as ultraviolet irradiation, DNA-damaging agents, inflammatory cytokines and oxidative stress while the activation of ERK cascade is often associated with growth factors. Following the response to a wide variety of stimuli, the activation of MAPK kinase kinase kinase (MAP3K) will lead to the phosphorylation and activation of MAPK kinase kinase (MAPKK). Then, the dual-specificity kinase MAPKK will activate MAPK via phosphorylation of tyrosine and threonine residues within a conserved Thr-Xaa-Tyr motif. Thereby, the activated MAPK signaling pathway induces apoptotic cascade in tumor cells [40, 41].

Table 4. The effects of melatonin on MAPK pathway

Tumor model	Mechanism(s) of action	Ref.
Gastric cancer cells	Activated the phosphorylation of p38, JNK and ERK	[35]
RKO colorectal cancer cells	Inhibited the p38 MAPK signaling pathway Decreased Rho-associated protein kinase expression Increased expression of zonula occludens-1 and occludin on cell membrane	[44]
SGC-7901 human gastric cancer cells	Elevated the expression levels of phospho-p38 and phospho-JNK protein	[43]
MiaPACA-2 human pancreatic carcinoma cells	Activated phospho-JNK and phospho-ERK ½ protein expressions	[31]
AsPc-1 and MiaPaCa-2 human pancreatic ductal adenocarcinoma cells	Decreased the expression level of phospho-p38	[22]

Studies of cancer cells have shown that melatonin treatment is associated with increased phosphorylation of JNK/SAPK and p38 MAPK proteins. This triggers the pro-apoptotic protein Bax expression and the cytochrome c release to cytosol, leading to the activation of caspases and results in apoptotic cell death [42]. The studies on gastric and pancreatic cancers further proved that melatonin could downregulate the NF-κB-p65 phosphorylation through the activation of JNK/SAPK and p38 MAPK [31, 43]. Subsequently, the expression of genes encoding various apoptosis-suppressor proteins is inhibited. Although the regulation of MAPK pathway is found to be associated with apoptotic cell death as shown in **Table 4**, the precise mechanisms whereby the activation and phosphorylation of p38 MAPK, JNK/SAPK and ERK in apoptotic cell death that are induced by melatonin are limited and require further elucidation.

Phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathway

The activation of PI3K/Akt signal transduction pathway in tumor cells plays a vital role in uncontrolled cell proliferation, oncogenesis, tumor angiogenesis and resistance to apoptosis [45]. Using human breast cancer MDA-MB-361 cell as experimental model, a study demonstrated that melatonin suppressed the PI3K/Akt signal transduction pathway by markedly inhibiting the phosphorylation of Akt, PI3K, glycogen synthase kinase (GSK)-3 and proline-rich Akt substrate of 40 kDa (PRAS40) proteins [17]. The inactivation of this pathway is associated with the attenuation of anti-apoptotic proteins Bcl-X_L and Bcl-2 which further reduces the cellular proliferation and enhances apoptotic action via mitochondrial pathway (**Table 5**).

Table 5. The effects of melatonin on PI3K/Akt pathway

Tumor model	Mechanism(s) of action	Ref.
MDA-MB-361 human breast cancer cells	Inhibited phosphorylation of PI3K, Akt, PRAS40, GSK-3 proteins Inactivated PI3K/Akt signaling pathway	[17]
HCT116 human colorectal adenocarcinoma cells	Increased the expression of p16 and phospho-p21 Suppressed phospho-Akt expression	[14]
HepG2 human hepatoblastoma cells	Decreased Akt phosphorylation	[37]

Nuclear factor kappa B (NF-κB) pathway

NF-κB is a transcription factor that belongs to the Rel family, which consists of p50, p52, c-Rel, RelB and p65. Generally, NF-κB dimer binds to NF-κB inhibitor (IκB) protein. Upon activation, NF-κB p65 is released from the IκB complex and translocates to the nucleus for the induction of gene expression of cell-cycle regulatory proteins, such as cyclin D1 and apoptosis-suppressor proteins, such as Bcl-xL and Bcl-2 [35, 43]. Melatonin was found to abrogate the acetylation and DNA binding activities of NF-κB as well as downregulate the phosphorylation of NF-κB p65 [35, 43]. These markedly reduce the cell viability and induce apoptotic cell death in several cancer cell lines listed in **Table 6**.

Table 6. The effects of melatonin on NF-κB pathway

Tumor model	Mechanism(s) of action	Ref.
SK-N-MC Ewing's sarcoma cells	Increased the activation of NF-κB	[25]
SGC-7901 human gastric cancer cells	Decreased the expression level of nuclear protein p65 and phospho-p65 Inhibited the translocation of NF-κB p65 from the cytoplasm to the nucleus	[43]
MiaPaCa-2 human pancreatic carcinoma cells	Inhibited NF-κB p65 activation	[31]

AsPc-1 and MiaPaCa-2 human pancreatic ductal adenocarcinoma cells	Decreased nuclear level of NF-κB/p65 with a concomitant decreased in the expression levels of phospho-NF-κB/p65 Supressed IκBα phosphorylation	[22]
KTC-1 and BCPAP human papillary thyroid cancer cells, 8505c and ARO human anaplastic thyroid cancer cells	Inhibited p65 phosphorylation and nuclear translocation Suppressed the expression of NF-κB/p65 and total phosphorylated NF-κB/p65 Downregulated interleukin-1α, Bcl-x, TWIST1, matrix metallopeptidase 9, cyclin D1 and CXC chemokine receptor 4	[33]

MDM2/AKT/p53 pathway

Mitochondrial apoptosis pathway is regulated by a number of upstream regulators including the protein serine/threonine kinase Akt (also known as protein kinase B), the human homologue of the mouse double minute gene (MDM2) and p53 tumor suppressor protein. The p53 tumor suppressor gene encodes for a transcription factor that regulates the cellular signaling cascades to execute apoptosis while MDM2 plays a central role in cancer progression by acting as the negative regulator of p53 tumor suppressor activity [46]. At the protein level, MDM2 inhibits p53 transcription activity and increases the ubiquitin-dependent proteolysis of p53. Furthermore, activation of PI3K and its downstream target can trigger the phosphorylation of MDM2 on serine 166 and serine 186. The phosphorylation at these specific sites is mandatory for nuclear translocation of MDM2, which subsequently degrades the p53. In response to cellular stress, the MDM2-mediated degradation of p53 is attenuated, resulting in cell cycle arrest or apoptosis [13, 46, 47]. As shown in **Table 7**, several studies reported that melatonin inhibited cancer growth by attenuating Akt activity which subsequently led to the inactivation of MDM2 and upregulation of p53 level.

Table 7. The effects of melatonin on MDM2/AKT/p53 pathway

Tumor model	Mechanism(s) of action	Ref.
MCF-7 human breast cancer cells	Downregulated MDM2 gene expression Increased L11 and inhibited Akt-PI3K-dependent MDM2 phosphorylation Increased in murine double minute X (MDMX) and p300 levels Decreased SIRT1 Enhanced p53 acetylation by modulation MDM2/MDMX/p300 pathway	[47]
SGC-7901 human gastric cancer cells	Attenuates the expression of MDM2, phospho-MDM2 (at Ser166), Akt and phospho-Akt (at Thr308) Increased the expression of p53	[13]
SOSP-9607 human osteosarcoma cell line	Downregulated SIRT1 signaling Upregulated acetylated-p53	[38]
OVCAR-429 and PA-1 ovarian cancer cells	Upregulated p27 and p53	[21]

Other pathways

A few alternative mechanisms of melatonin's anti-proliferative and pro-apoptotic effects have been observed in a large variety of cancer cell types as listed in **Table 8.** A study has revealed that melatonin decreased cell viability of MDA-MB-231 cells via downregulating the phosphorylation of proteins in mTOR/Akt/STAT3 pathway [15]. Furthermore, melatonin is shown to be pro-apoptotic on HepG2 cells by significantly reducing the phosphorylation of Forkhead box O3a (FoxO3a) at Thr32 and Ser253, increasing the total protein of FoxO3a, upregulating the expression of Bim and decreasing the Akt phosphorylation [37]. Besides, melatonin induced apoptosis in colorectal cancer LoVo cells through dephosphorylation and nuclear import of histone deacetylase 4 (HDAC4), subsequently lead to H3 deacetylation via the inactivation of Ca^{2+}/calmodulin-dependent protein kinase II alpha (CaMKIIα) [29]. Another study reported that melatonin induced the apoptosis of HepG2 and SMMC-7721 cells by downregulating the expression of survivin and X-linked inhibitor of apoptosis (XIAP). Both survivin and XIAP are the inhibitor of apoptosis proteins (IAPs) which act as the key regulators of caspase for the execution of apoptosis [48].

Table 8. The effects of melatonin on other pathways

Tumor model	Mechanism(s) of action	Ref.
mTOR/AKT/STAT3 pathway		
MDA-MB-231 human breast cancer cells	Downregulated the phosphorylation of Akt, mTOR and Signal transducer and activator of transcription 3 (STAT3) Activated cleaved PARP and caspase	[15]
ER stress-induced apoptosis		
HepG2 human hepatoma cell line	Selectively blocked activating transcription factor 6 Increased C/EBP homologous protein (CHOP) level Inhibited cyclooxygenase (COX)-2 expression and enhanced cell apoptosis	[36]
HepG2 and SMMC-7721 hepatocellular carcinoma cells	Reduced the expression of COX-2 Induced apoptosis via COX-2/PI3K/Akt pathway	[48]
A2780 ovarian carcinoma cells	Increased endoplasmic reticulum stress and induced apoptosis via calcium release from endoplasmic reticulum Increased expression of inositol 1,4,5-trisphosphate receptor type1 (IP3R1)	[49]
Inhibitor of apoptosis proteins		
HepG2 and SMMC-7721 hepatocellular carcinoma cells	Downregulated the expression of Survivin and XIAP but not cellular inhibitor of apoptosis protein (cIAP)-1 and cIAP-2	[48]
FoxO3		
HepG2 human hepatoblastoma cells	Reduced phosphorylation of FoxO3a at Thr32 and Ser253 Increased protein level of FoxO3a total form	[37]

CONCLUSION

Owing to the chemopreventive, tumor growth inhibitory and oncostatic properties in a wide variety of neoplasia, melatonin has been studied for the past decades in *in vitro* experimental models. Different mechanisms involved in tumor growth inhibitory and apoptotic effects of melatonin in *in vitro* models have been identified and documented. Generally, melatonin is able to trigger cell cycle arrest and apoptosis in tumor cells via multiple apoptotic signaling pathways, including the death receptor pathway, mitochondrial pathway, MAPK pathway, PI3K/Akt pathway and NF-κB pathway. Also, the activation of pro-apoptotic Bcl-2 family proteins induced by melatonin can activate the apoptotic cascade in cancer cells. Melatonin has been demonstrated to have no cytotoxic effect in normal cells [50,51]. Therefore, melatonin can be a potential adjuvant drug for the treatment of cancers.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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