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Targeting cancer stem cells by melatonin: Effective therapy for cancer treatment

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ABSTRACT

Melatonin is a physiological hormone produced by the pineal gland. In recent decades, enormous investigations showed that melatonin can prompt apoptosis in cancer cells and inhibit tumor metastasis and angiogenesis in variety of malignancies such as ovarian, melanoma, colon, and breast cancer; therefore, its possible therapeutic usage in cancer treatment was confirmed. CSCs, which has received much attention from researchers in past decades, are major challenges in the treatment of cancer. Because CSCs are resistant to chemotherapeutic drugs and cause recurrence of cancer and also have the ability to be regenerated; they can cause serious problems in the treatment of various cancers. For these reasons, the researchers are trying to find a solution to destroy these cells within the tumor mass. In recent years, the effect of melatonin on CSCs has been investigated in some cancers. Given the importance of CSCs in the process of cancer treatment, this article reviewed the studies conducted on the effect of melatonin on CSCs as a solution to the problems caused by CSCs in the treatment of various cancers.

1. Introduction

Cancer is one of the central and complex health concerns, which has the second rank after heart disease among the causes of patient mortality [1,2]. In previous decades, researchers tried to understand developmental and progression mechanisms of cancer, and also evaluate novel therapeutic actions counter to cancer [3]. These studies have led scientists to discover that, cancer is generated by a group of cells with stem cell traits termed cancer stem cells (CSCs) [4]. For the first time, Bonnet et al. proposed the presence of CSCs in a tumor population. Accordingly, they recognized a small group of cell in leukemia tumor with similar features to the normal stem cells [5]. CSCs are identified with slow cell cycles and motile state, the capability to self-renewal, and differentiate for tumor development [6]. Approximately 0.01–1.0 % of cells in tumor mass are CSCs and were identified in a number of tumors such as breast [7], colon [8], ovarian [9], lung [10], and head and neck carcinomas [11]. Stem-ness pathways, such as wingless-related integration site (Wnt), transforming growth factor beta (TGF-β), signal transducer and activator of transcription (STAT), and Hippo-YAP/TAZ are involved in the features of CSCs such as self-renewal and differentiate for tumor development [12]. Unlike normal stem cells (NSCs) that have stringently regulated stem-ness pathways, CSCs have highly deregulated stem-ness pathways [13]. Moreover, the ability of tumor metastasis and invasion, and resistance to cancer chemotherapy

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may be due to existence CSCs [14]. Since the important traits of CSCs such as poor prognosis, drug resistance, invasive and metastatic capability, self-renewal ability, targeting CSCs can be considered as a promising treatment in cancer therapy.

Melatonin or N-acetyl-5-methoxytryptamine is a physiological hormone produced by the pineal gland. The pineal gland secretes melatonin into the blood circulation, and melatonin shows a range of physiological actions including sleep regulation and circadian rhythms, effect of reproduction system, effect on bones, and affecting the aging and immune system [15]. Furthermore, in recent decades, performing enormous investigations showed that, melatonin can prompt apoptosis in cancer cells, block tumor metastasis, and angiogenesis in variety of malignancy such as ovarian, melanoma, colon, and breast cancer; therefore, its possible therapeutic usage in cancer treatment was confirmed [15,16].

Melatonin can act by a link to membrane receptor (MT1 and MT2) or nuclear receptors (RZR/RORα: orphan *nuclear receptor* ROR alpha) [17]. Moreover, melatonin can act trough receptor-independent manner including antioxidant and free radical scavenging properties [18]. Recently, the role of melatonin in the regulation of viability, proliferation, and apoptosis of CSCs has been suggested. Recent documents proposed that, the antitumor properties of melatonin are due to its cytotoxicity prompted in CSCs of the brain [19], glioblastoma [20], breast [16], melanoma [21], colorectal [19], ovarian [15], and osteosarcoma [22]. The aim of this study was to provide an overview on targeting CSCs by melatonin as a therapeutic action for the cancer treatment. Moreover melatonin can act trough receptor-independent manner include antioxidant and free radical scavenging properties. Recently, the role of melatonin in regulation of viability, proliferation and apoptosis of CSCs has been suggested. Recent documents proposed that the antitumor properties of melatonin are due to its cytotoxicity prompted in CSCs of the brain, glioblastoma, breast, melanoma, colorectal, ovarian and osteosarcoma (Table 1 & Fig. 1). The aim of this study is to provide an overview about targeting CSCs by melatonin as a therapeutic action for cancer treatment.

2. The origin of cancer stem cell and identification methods

There is three possible theories about the source of CSCs: normal stem cells transformed to CSCs, adult cells transformed into stem cells by epithelial to mesenchymal transition (EMT) and induced pluripotency in cancer cells [23].Several proteins expression is linked with CSCs traits. One of the items to identify CSCs is cell surface antigens that mainly to the group of membrane proteins. The first study that identified CSCs with surface marker was in acute myeloid leukemia (AML). In this study AML CSCs were defined with phenotype of CD34 + /CD38 − [24] After that other researcher try to use surface markers to recognize CSCs in other tumors. Other surface markers that have been used for identification of CSCs include CD133 (prominin-1), CD24, CD13, CD16, CD38, CD34, CD44, EpCAM/ESA (epithelial-specific antigen), CD166,CD90, CD176, CD20, and CD66c alone or in combination [5]. In addition to the surface markers used to identify and isolate CSCs, spheroid formation assay, colony formation assay, label-retaining methods, Aldehyde dehydrogenases (ALDHs) activity, Side Population (SP) assay, CSC selection by natural killer cells, also used for identification and isolation of CSCs [5].

3. The role of CSCs in patient prognosis

Nowadays, the use of CSCs and their markers in the prognosis of cancer patients has been considered by researchers and physicians.The relationship between CD133 and poor prognosis in cancer of the colorectal [25,26], brain [27], liver [28], stomach [29], endometrium [30], ovary [31], and lung [32] was confirmed. Furthermore, high expression of CD133 is an adverse prognostic indicator in pancreatic cancer that associated with lymph node invasion. Another marker considered as a prognostic marker is CD44. Overexpression of CD44 is linked with poor prognosis in hepatocellular carcinoma and led to reduced disease-free and overall survival of patients [33]. Also, overexpression of CD44 was correlated with decreased overall survival in pancreatic cancer patients [34]. CD24 that use for identification and

Table 1
Summary of antitumor effects of melatonin in various cancers via targeting CSCs.

Type of cancer	CSCs isolation markers	The dose of Melatonin	The beneficial effect of melatonin on CSCs	Ref.
Breast cancer	CD44 + CD24-	1 Mm 35uM	- Reduction in mamospheres's size - Increases expression of E-cadherin - Reduces the expression of OCT4, N-cadherin, vimentin, - Induction of autophagy	[16,51]
Lung cancer	Sca-1$^+$/CD34$^+$, CD133$^+$	0.1-0.3-1 mM	- Reduces expression of CD133 marker - Regulation of ERK/p38, PLC, Twist, and β-catenin signaling pathways	[80]
Melanoma	CD271,CD24,CD133	1.0 mM	- Reduces cancer cell proliferation and self-renewal capability. - Reduces hTERT expression.	[21]
Glioma and brain	CD133, CD15/ Stage-specific embryonic antigen (SSEA), CD44, A2B5	1mM 0.5 mM	- Synergistic toxic effect with temozolomide in BTSC via regulation of ABCG2/BCRP transporter expression. - Decreases proliferation through inhibition of TFEB, up-regulation of pre-apoptotic genes, activation of apoptosis process. - Inhibition of the AKT-EZH2-STAT3. - Regulation of EZH2-NOTCH1. - Regulation of ABCG2/BCRP transporter expression. - Suppression of Nestin and c-Myc.	[52,81,82]
Colorectal cancer	CD44 + , CD66c	0.5 mM	- Stimulation of apoptosis and autophagy via modifying the OCT4-PrPC axis	[72]
Osteosarcoma	CD117 + , CD133 + , CD117$^+$ Stro-1$^+$, CD49f$^-$ CD133$^+$	0.5 mM	- Controls the level of phosphorylated ERK, β-catenin, SOX9	
Ovarian	CD44 + CD117 + , CD24 + , CD133 + ,	3.4 mM	- Down-regulation of EMT-related proteins (vimentin, snail, ZEB1 and ZEB2) - Inhibited activity of MMP-9	[15]

CSCs: Cancer Stem Cells,**OCT4:** Octamer-binding transcription factor 4, **ERK**: Extracellular signal–regulated kinase, **PLC**: Phospholipase C, **hTERT**: human telomerase reverse transcriptase, **BTSC**: Brain tumor stem cell, **ABCG/BCRP**: ATP-binding cassette super-family G member 2/ Breast Cancer Resistance Protein, **TFEB**: transcription factor EB, **EZH2**: Enhancer of zeste homolog 2, **STAT3**: Signal transducer and activator of transcription 3, NOTCH1: Neurogenic locus notch homolog protein 1, **PrPc**: Cellular prion protein, **SOX9**: SRY-Box Transcription Factor 9,**ZEB1**: Zinc Finger E-Box Binding Homeobox 1, **ZEB2:** Zinc Finger E-Box Binding Homeobox 2, **MMP-9**: Matrix Metallopeptidase 9.

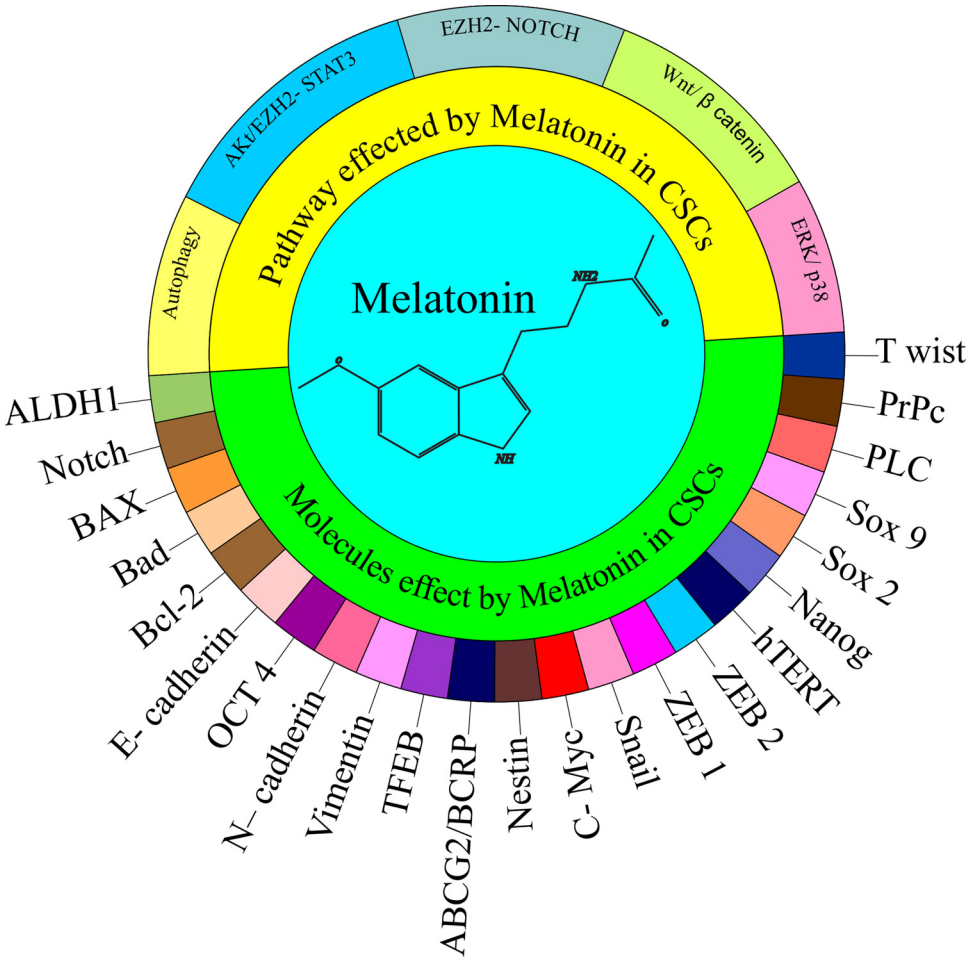

Fig. 1. Schematic overview of molecules and signaling pathways involved in the antitumor effects of melatonin by targeting cancer stem cells. **CSCs:** Cancer Stem Cells,**OCT4:** Octamer-binding transcription factor 4, **ERK**: Extracellular signal–regulated kinase, **PLC**: Phospholipase C, **hTERT**: human telomerase reverse transcriptase, **ABCG/BCRP**: ATP-binding cassette super-family G member 2/ Breast Cancer Resistance Protein, **TFEB**: transcription factor EB, **EZH2**: Enhancer of zeste homolog 2, **STAT3**: Signal transducer and activator of transcription 3, NOTCH1: Neurogenic locus notch homolog protein 1, **PrPc**: Cellular prion protein, **SOX9**: SRY-Box Transcription Factor 9,**ZEB1**: Zinc Finger E-Box Binding Homeobox 1, **ZEB2**: Zinc Finger E-Box Binding Homeobox 2, **BAX:** Bcl2-associated X protein, **Bad:** Bcl-2 antagonist of cell death.

isolation of CSCs is a highly glycosylated mucin-like antigen on the cell surface and newly appeared as a unique prognosis marker. *Jing X* et al. suggested that high expression of CD24 is more common in breast cancer tissues than in normal breast tissue. Additionally, CD24 can function as prognostic marker for breast cancer [35]. As previously discussed, there is relation among the expression of aldehyde dehydrogenase-1 (ALDH1), the stem-like feathers and chemo-resistance in breast cancer. *Muhammad Alamgeer* et al. reported that the expression of ALDH1 is a valuable predictor of chemo-resistance. The high expression of ALDH1 led to poor survival in locally advanced breast cancer [36].Also, *Tingting Yao* et al. confirmed positive correlation between ALDH1 and poor prognosis in cervical cancer [37]. Concerning the mentioned, CSCs can be considered as an important factor in the prognosis of patients. In the following, we will discuss the effect of melatonin on CSCs in various cancers.

4. Melatonin and breast cancer stem cell

Breast cancer is the first leading cause of cancer death among women worldwide [38]. Risk of breast cancer varies 5-fold among countries, is increasing everywhere, and is highest in the industrialized nations. Breast cancer has a high rate of mortality and morbidity mainly due to the tumor recurrence and metastasis [39,40]. A high prevalence of CSCs in breast primary tumors, which may be identified by CD44+/ CD24- markers, is linked with the occurrence of distant metastasis [41]. ALDH is one of the important markers for detection and isolation of breast CSCs (BCSCs) [5]. An association observed between expression of this marker and increased distant metastasis and lower survival rate in patients' samples of inflammatory breast cancer [42]. The octamer-binding transcription factor 4 (OCT4) gene a member of the POU family is the master gene that plays a key role in the self-renewal and pluripotency of BCSCs [43]. Based on the idea that breast cancer treatment is particularly complicated by CSCs, and that the control of the disease requires the inhibition of these cells, recently, special attention has been paid to the effect of melatonin on BCSCs, and studies have been done in this regard.

Melatonin may suppress multiple central molecular mechanisms linked to tumor stem cell self-renewal, viability, invasiveness, tumor growth, and chemo-resistance. *Do Nascimento Gonçalves* and colleagues showed that melatonin has an inhibitory role on the viability and invasiveness of breast cancer mammospheres (representing the CSCs population). The mechanism of this inhibition is by applying changes to the genes and proteins involved in the EMT and markers related to CSCs. Observations of this study indicate that melatonin increases expression of E-cadherin and reduces the expression of OCT4, N-cadherin and vimentin, signifying its possible anti-metastatic action [16].

On the other hand, one of important factors in genesis and evolution of mammary tumors is estrogen and undeniable as nearly 80 % of breast tumors are classified as estrogen receptor (ER) positive. The documents showed that melatonin as a natural substance may be useful in prevention and treatment of estrogen related breast cancer in different ways (i) by down-regulating gonadal synthesis of steroids and, consequently, decreasing their circulating levels; (ii) by interacting with the ER; and (iii) by down-regulating the activity of some enzymes [44]. Additionally, an important interaction of melatonin with estrogen-mediated mechanisms of MCF-7 cell proliferation has been proved [45]. Beside the estrogen-mediated mechanisms of melatonin on breast cancer treatment, its effect on BCSCs has been studied recently. In an in-vitro study the breast cancer was initiated by administrating estrogen (E2) and environmental estrogen bisphenol A (BPA). Treatment with

melatonin caused reduction in mamospheres's size, and also decreased binding of ER-alpha to OCT4 accompanied by reduction of ER-alpha and OCT4 expression in MCF-7 line cells [46]. Another treatment choice can be associated with the mechanisms that can affect the stem cell's origination. As previously mentioned, CSCs are generated via EMT. Melatonin has modulatory effects on the expression of proteins related to EMT in breast CSCs like EMT molecular markers: OCT4, E-cadherin, N-cadherin and vimentin. Moreover, melatonin treatment has inhibitory effects on the viability and invasiveness of both canine and human breast cancer mamosphere [16]. Another mechanism may be the protective effect of melatonin on induced autophagy in CSCs. It has been demonstrated that melatonin has pro-autophagic effects on stem cells with $CD44^{+}CD24^{-/low}$ obtained from a breast cancer cell line (MCF-7) [47].

Documents showed that the BCSCs are responsive to melatonin treatment, reducing the viability and the invasiveness cellular capacity, as well as, the expression of stem cell and EMT markers. In addition, due to the BCSCs being highly resistant to chemotherapy, drugs that act successfully on this subpopulation can represent an effective therapeutic option for the breast cancer patient and melatonin may be one of them.

5. Melatonin and glioblastoma cancer stem cells

Glioblastoma is a common brain tumor with a high mortality and short life expectancy average. The evidence demonstrated that glioblastoma stem-like cells (GSCs) play a critical role in tumor growth, tumor recurrence, therapeutic resistance, and post-therapy relapse [48]. Surface markers such as CD133, CD15/ Stage-specific embryonic antigen (SSEA), CD44, or A2B5 in different researches were used for GSCs isolation. Due to inefficiency of current therapeutic methods in eliminate GSCs subpopulations, new therapeutic strategies are urgently needed in treatment of glioblastoma [49]. Previous studies reported that melatonin significantly decreases proliferation of glioblastoma cells and GSCs both in vivo and in vitro. Furthermore, melatonin decreases clonogenic and self-renewal capability of GSCs through induction of differentiated markers and inhibition of stem cell markers [50,51]. In a recent study by *Sung* et al. reported that melatonin may decreases proliferation of GSCs through inhibition of transcription factor EB (TFEB), which leads to up-regulation of pre-apoptotic genes and activation of apoptosis process. Moreover, melatonin reduces tumorigenicity of GSCs through inhibition of the AKT-EZH2-STAT3 signaling pathway, which involved in CSCs proliferation and carcinogenesis [52]. In another study by *Zheng* et al. reported that melatonin reduces proliferation and self-renewal capability of GSCs through regulation of EZH2-NOTCH1 signaling pathway. Furthermore, evidence showed that melatonin increases efficacy of brain tumor stem cells (BTSCs)-targeted chemotherapeutic agents through regulation of ABCG2/BCRP transporter expression [53]. In a recent study by *Lee* et al. reported that melatonin synergistically increase brain CSCs sensitivity to Paclitaxcel through suppression of Nestin and c-Myc [54]. These cellular events demonstrate a wide alteration in transcriptional program and suggest that melatonin involve in cellular reprogramming events, such as activation of specific genes and acquisition of transcriptional competency. However, the exact effect melatonin on GSCs and underlying action mechanisms are largely unknown.

6. Melatonin and ovarian cancer stem cells

Although ovarian cancer (OC) is not the most common cancer in the world, it has a high mortality rate, as about 70 % of cases are likely to have recurrent ovarian cancer symptoms and drug resistance. Epithelial ovarian cancers are the most common type of ovarian malignancy because they usually do not have clinical symptoms until metastasis, and more than two thirds of patients are at advanced stages of diagnosis. Although surgery and conventional chemotherapy are effective in treating ovarian cancer in the early stages, resistance to this type of chemotherapy may recur. Drug resistance can be due to exciting ovarian CSCs in ovarian cancer. Some marker have been used to isolation and identification of CSCs in ovarian cancer such as $CD44+CD117+$, $CD24+$ and $CD133+$. Baba et al. showed that $CD133+$ cells could form more aggressive tumor xenografts [55]. Therefore, developing effective treatment strategies can be critical in ovarian cancer therapy. Melatonin secretion has been performed through granulosa cells of pre ovulatory follicles in normal ovary [56]. Melatonin has high potential for free radical scavenger and motivates the activity of antioxidant enzymes in the ovary. Production of reactive oxygen species (ROS) through ovulation can be modify transformation of tubal fimbria cells with p53 loss, whereas melatonin eliminated the tumorigenic outcome prompted via ROS [57].

Previous studies suggested that the activity and expression of matrix metalloproteinases (MMPs) were related to the stem-ness properties of CSCs. In this regards *Akbarzadeh* et al. suggested that melatonin constrains invasion of CSCs via down-regulation of EMT-related proteins (vimentin, snail, Zinc finger E-box binding protein 1(ZEB1) and ZEB2) and activity of MMP-9 but not MMP-2. Also, their result showed that the expression of ZEB1, ZEB2, Snail and vimentin in ovarian CSCs was significantly higher than SKOV3 cells, whereas E-cadherin marker was higher in SKOV3 epithelial cells [15]. The study by *Akbarzadeh* et al. was the only study to examine the effect of melatonin on CSCs, and it is clear that detailed studies are needed to elaborate.

7. Melatonin and melanoma cancer stem cells

Melanoma, a kind of skin cancers, is one of the most threatening and drug-resistant of human cancers which arising from uncontrolled proliferation of melanocytes [20]. According to the studies, the median and long term survival rate for patients with metastatic melanoma is less than 1 year and only 5 % respectively [58,59]. Due to the aggressiveness, melanoma is often diagnoses at the advanced stages and the general treatments, surgery and radio/chemotherapy, are not respond. Since 2011, treatment of melanoma, targeted therapies and immunotherapy, has been revolutionized as a result of better understanding of cancer biology and immunology [60]. Although appearance and widespread application of the combinational immunotherapy has been led to significantly progression of melanoma treatment, more explorations are necessary to find out other treatment options to reach better clinical outputs because the response rates to immunotherapy are not satisfied yet.

Growing bodies of cancer studies have been shown that challenges in melanoma treatment can be due to melanoma CSCs [61]. Melanoma CSCs can be characterize and isolate by specific surface markers however, because of the high degree of plasticity of melanoma cells, and some mechanisms that leading to the progression of melanoma, the characterization of the unique and specific biomarkers for melanoma stem cells is still controversial [62], however some of melanoma CSCs markers summarized in Table 2. Melanoma CSCs by overexpression of the anti-apoptotic proteins as well as Bcl-2, factors involved in the regulation of the apoptosis signaling, and activating some signaling pathways for example Notch/Hedgehog, and DNA damage repair capability, have been shown resistance to chemo and radiotherapy respectively [62]. CSCs were reported to be involved in the resistance of melanoma malignant cells to the standard therapeutics for example taxanes and dacarbazine [63]. The mitogen associated protein kinase (MAPK) signaling pathway activates BRAF signaling pathway leading to the activation of MEK and finally phosphorylation and activation of ERK [21]. As previous study declared, in BRAF mutated melanoma cells, resistance to BRAF and MEK inhibitors is associated with elevated expression of Sox2 and CD24, its downstream target gene. In the study which done by *Cordaro* and his Colleagues, they demonstrated resistance of melanoma cells to dabrafenib, display stem-ness feature, activation of the transcription factor OCT4 and finally over expression

Table 2
Melanoma CSCs molecules are used in melanoma malignant cells characterization.

Molecule Name	Associated properties and function	References
CD133	• Tumor initiation • Maintain long-term tumorigenic potential • p38 MAPK pathway activation • Induction of angiogenesis and metastasis • Melanoma CSCs isolation • Chemoresistance	[83]
CD271	• Tumor initiation • Associated with metastasis • Establish tumor heterogeneity • Maintain long-term tumor growth	[84]
ALDH	• Self- generation and differentiation • Multidrug resistance • Immunological resistance	[85]
CD24	• Chemoresistance • Melanoma progression	[86]
CD20	• Highly enrich in melanosphere • Self- renewation • Melanoma growhing	[87]
CXCR6	• Self- generation • Highly tumorigenic	[88]
JARID1B(histone demethylase)	• Give rise to highly proliferative progeny • Self- generation • Tumor progression and metastasis • Regulation of Jagged1/Notch1 signaling pathway	[89]
Nanog, OCT3/4	• Melanoma CSCs progression	[90]
Wnt, Notch, HedgeHog	• Tumor progression	[91]
ABCB1, ABCB5, BCG2	• Drug resistance • Tumor initiation • Self-renewal and differentiation • Tumor progression • Co-expression with CD133	[92]
Sox 2, 10	• Tumor initiation and progression	[93]

CSCs: Cancer Stem Cells, **OCT3/4:** Octamer-binding transcription factor 4, **ABCB5**: ATP-binding cassette super-family B member 5, **NOTCH1**: Neurogenic locus notch homolog protein 1, **SOX2**: SRY-Box Transcription Factor 2, **SOX9**: SRY-Box Transcription Factor 9, **MAPK**: Mitogen-activated protein kinase, **VEGFR1**: Vascular endothelial growth factor receptor 1, **CXCR6:** C-X-C Motif Chemokine Receptor 6, **WNT**: Wingless family.

of CD20 marker [64]. Therefore, the designing of more effective therapeutic strategies that targeting melanoma stem cells and associated molecular pathways can be considered as a novel strategy in melanoma treatment.

It is interesting to note that melatonin reduces cancer cell proliferation and self-renewal capability through the diminishing the expression of stem cell markers. As mentioned in publications, there are relation between human telomerase reverse transcriptase (hTERT) expression and outcomes in patients with melanoma [65]. Additionally, hTERT has functionally role in the maintenance of stem-ness in cancer cells [66]. Notably, melatonin through decreasing the expression of stem cell markers such as hTERT leading to reduction of cancer cell proliferation, clonogenic capability and self-generality. It has been reported that melatonin by targeting Nanog, Sox2 and OCT4, the stem-ness-associated transcription factors, Notch and Wnt/β-catenin, CSC progression pathways, and molecules that are involve in induction of apoptosis for example Bax, Bad and Bcl-2 are able to aff ;ect the survival and self-renewal of melanoma CSCs [21]. However, now day, very few studies have investigated the therapeutic effects of melatonin on melanoma CSCs. Therefore, it is important to clarify the underlying molecular mechanism and therapeutic effects of melatonin in melanoma treatment.

8. Melatonin and colorectal cancer stem cells

Colorectal cancer is the second and third cause of cancer-related receptively in men and the women worldwide [67]. In the field of colorectal cancer treatment such as surgical skills, chemotherapy, and tumor molecules targeting significant advances have been made, however researchers have not been fully successful in its treatment [68]. A main challenge in colorectal cancer treatment is drug resistance. Due to the characteristics of cancer stem cells, it may be the drug resistance created in colorectal cancer is due to the presence of CSCs [69]. For example, OCT4, a cancer stem cell marker, prompts and keeps pluripotency in colorectal cancer stem cells. In addition, OCT4 inhibits apoptosis induced via chemotherapy in colon cancer stem cells. Also the role of OCT4 in EMT, cell migration, invasion, and metastasis in colorectal cancer cells was confirmed. So, OCT4 have a critical function in colorectal cancer progress comprising tumor initiation, metastasis, and chemo-resistance [70]. Therefore, the discovery and development of novel therapeutics and molecular targets are essential in the treatment of colorectal cancer. In this regard, studies exposed that melatonin suppresses human colorectal cancer cell growth via enhancing production ROS. Moreover melatonin can prompts apoptosis, autophagy, and senescence in tumor cells. In addition, melatonin led to cell death in drug-resistant colorectal cancer cells. Furthermore, melatonin shows anti-metastatic effect on colorectal cancer by effecting cell-cell- and cell-matrix connections, altering the extracellular matrix, restructuring the cytoskeleton, modifying epithelial-mesenchymal transition, and inhibiting angiogenesis [71]. These findings suggest that melatonin is a potential therapy for colorectal cancer.

Melatonin is likely to have an effect on CSCs in colorectal cancer. In this way, *Casado* et al. showed that Arylalkylamine N-acetyltransferase (AA-NAT) (a regulator enzyme in melatonin synthesis pathway), MT1, and MT2 expression reduced in tumor tissues versus normal mucosa tissues in mutated p53 tumors in comparison with those with wild-type p53. Further, AA-NAT and MT2 expression were lesser in advanced stages of the disease in wild-type p53 tumors. Patients with CD44highCD66c high and wild-type p53 tumors in progressive stages exposed low expression of AA-NAT and MT2 in wild-type p53 tumors. These data suggest an interaction of these pathways in colorectal cancer stem cells [72]. Therefore, some studies have investigated the effect of melatonin on colorectal cancer stem cells.

Lee et al. reported a reduction in cellular prion protein (PrPC) and the stem cell marker OCT4, Nanog. Sox2, and ALDH1A1 expression through co-treatment with 5-FU and melatonin. They also showed that 5-FU and melatonin stimulate apoptosis and autophagy in colon CSCs via modifying the OCT4-PrPC axis. A highly ubiquitous glycoprotein, PrPC, is expressed in nerve cells and other tissues. Several researches shows the role of PrPC in tumor behavior such as proliferation, apoptosis, invasion, metastasis, and chemo-resistance. Also, PrPC participated in cancer cell self-renewal. Noticeably the association between metastasis and PrPC expression in CD44-positive colon CSCs was reported [19]. Thus, it is likely that there is a relationship between melatonin and its inhibitory effects on colorectal cancer stem cells, although studies are limited and further studies are needed.

9. Melatonin and osteosarcoma cancer stem cells

Osteosarcoma is one of the most prevalent primary tumors of bone in adolescents. Osteosarcoma is an aggressive malignancy with the origin of abnormal transformation of mesenchymal cells, showing the osteoblastic differentiation and formation of malignant osteoid [73]. In osteosarcoma, main fatal reason is lung metastasis, which can scarcely be treated by existing chemotherapeutic agents [74]. It was suggested that, the reason of metastasis in osteosarcoma is the existing of osteosarcoma cancer stem cells. It has been showed that, in several human osteosarcoma cell lines, cells with CD133+ phenotype exhibiting stem-like characteristics [75]. Previously, it has been reported that,

melatonin is intimately associated with bone metabolism and suppress the growth of osteosarcoma cells. *Qu* et al. also reported that, the treatment with melatonin considerably decreased the proportion of CD133+ CSC-like cells. Also, melatonin treatment adversely controls the levels of phosphorylated ERK, β-catenin, and SRY-Box Transcription Factor 9 (SOX9), which are intricate in the process of EMT. Also, overexpressing SOX9 can assist the self-renew and increase the proportion of CD133+ cells [76].

Therefore, it can be concluded that melatonin can indeed impede the migration and invasion of osteosarcoma to a certain extent by inhibiting CSC. However, similar to other tumors, the data on the effects of melatonin and osteocarsinoma is limited, and the underlying action mechanisms are largely unknown yet.

10. Melatonin and lung cancer stem cells

Lung cancer is one of the most important malignancy with high cancer-related morbidity and mortality in the world [77]. The stem-cells like with high tumorigenic capability and unlimited self-renewal are responsible for metastatic dissemination and post-therapy relapse in lung cancer. Therefore, various compounds and drugs that attack lung CSCs have therapeutic benefit in lung cancer [78]. The evidence demonstrated that lung CSCs are responsible for EMT properties during metastasis of lung cancer [79]. In the only study by *Yang* et al. suggested that melatonin reduces expression of lung CSCs CD133 marker and lung cancer stem-ness through regulation of ERK/p38, phospholipase-C (PLC), Twist, and β-catenin signaling pathways [80]. However, the exact effect melatonin on lung GSCs and underlying action mechanisms are largely unknown. These evidences provide an insight of the melatonin as a novel agent against lung GSCs.

11. Conclusion

The oncostatic effects of melatonin, a hormone of pineal gland, has been proven in both in vitro and in vivo studies. This hormone acts as inhibitory agent in cancer through a multiple mechanisms such as anti-proliferative actions, regulation of oncogenes expression, and anti-oxidant and anti-angiogenic effects. According to these features, researchers mostly tempt to try the effect of melatonin on CSCs. CSCs could lead to a complex challenge in cancer treatment, because of its resistant to chemotherapy and self-renewal. Based on the idea that cancer treatment is particularly complicated by cancer stem cells, researchers try to find therapeutic agent that can trigger CSCs. The data obtained from studies demonstrated that melatonin, as a tumor inhibitor, can target CSCs in some cancers such as glioma, breast, ovarian, colon, and osteocarcinoma. Melatonin can also regulate the main signaling pathways linked to self-renewal and survival of CSCs. In conclusion, melatonin may act as a promising therapeutic agent in cancer treatment by targeting CSCs. However, for the clinical use of melatonin in the cancer treatment, the concentration used in vitro studies is much higher than the concentration used for the patients. So it is necessary to determine the effective concentration through local drug delivery, which needs performing further studies in future.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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