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# Molecular and cellular mechanisms of melatonin in breast cancer

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ABSTRACT

Breast cancer is considered as one of the most important health problems due to its poor prognosis and high rate of mortality and new diagnosed cases. Annually, a great number of deaths are reported in men and women; this means that despite all the improvements in cancer diagnosis and treatment, still, an intense need for more effective approaches exists. Melatonin is a multivalent compound which has a hand in several cellular and molecular processes and therefore, is an appropriate candidate for treatment of many diseases like cancer. Currently, considerable properties of this agent have oriented the research towards investigating its effects specifically in breast cancer. In this review, we gathered a bunch of evidence in order to give a new sight for breast cancer treatment utilizing melatonin. We expect that in coming years, melatonin will become one of the most common therapeutic drugs with lesser side-effects than other chemotherapeutic drugs.



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## 1. Introduction

### 1.1. What is melatonin?

25 years ago, it was discovered for the first time that the hormone secreting from pineal gland has more functions than regulating the circadian rhythm. Many tasks such as skin recovery, changing skin color in amphibians [1], and scavenging free radicals are attributed to melatonin. Melatonin exert its roles by binding to its cell membrane receptors: melatonin receptor (MT) 1 to 3 [2,3]. These receptors are coupled to G-proteins that after the attachment of melatonin to its receptors, are activated. Klosen and colleagues explored melatonin receptors work and revealed that melatonin binds to MT1 and MT2 with a high affinity and MT2 is expressed in a diverse range of cells despite MT1 [4]. There are some signaling pathways that mediate the functions of melatonin after its linkage to MT1 or MT2. Two classes of these pathways can be found: cAMP-dependent and cAMP-independent [5]. In the former type, $G_i$ which is one of the connected G-proteins to the MT1 is activated. This event results in adenylate cyclase suppression and decreased extents of cAMP [6]. As a consequence, the cAMP-dependent signaling pathway is triggered [6]. The latter mechanism is attributed to mitogen activated protein kinase (MAP-K) signal transduction pathway. In this pathway, after the phosphorylation of GPCRs, MEK\ERK signaling cascade is activated [7]. Finally, through these receptors and signaling pathways, melatonin is able to affect several cellular processes including apoptosis, proliferation, inflammation, angiogenesis, and etc. and that's why this beneficial agent is being used for treating some diseases such as cancer [8–11].

### 1.2. Breast cancer: types, risk factors, and mechanisms

Generally, the name of breast cancer is not pointing to a specific disease with unique histological and biological features and it includes a wide range of different diseases [12]. Beside the mentioned characteristics, these diseases have even some differences in clinical signs and symptoms and their response to common therapies [12]. Due to the wide range of diversity in these cancers, several ways of classifications based on different properties exist [13,14]. One of these classifications is based on molecular aspects such as dysregulation in the estrogen receptor or ER and the human epidermal growth factor receptor 2 or HER2 [12,15]. According to this categorization, four types are enumerate for most of the breast cancers: HER2, luminal, basal-like, and normal breast-like [15].

In the disease-causing point of view, there are some factors that are acknowledged to be associated with a higher risk of breast cancer. These factors encompass sex, age, disease history of family, late menopause, early menarch, excessive amounts of estrogen, and alcohol [16,17]. From the perspective of diagnosis and detection, besides physical examination, some imaging methods such as ultrasonography, mammography, MRI, and PET scan, using some biomarkers such as microRNAs are proven to be effective, and biosensors [18–21]. For the treatment of BC, the most common procedures contain surgery, radio and chemotherapy, immunotherapy, hormone therapy, antiHER2 therapy (as reviewed by Suter and Pagani) [22]. Nevertheless, the explorations for more diagnostic and therapeutic strategies are still not ended due to the high rate of breast cancer mortality.

## 2. Melatonin and breast cancer: mechanisms

Herein, we discuss a bunch of mechanisms that are included in both melatonin functions and breast cancer pathogenesis. In other words, investigating pathogenesis of breast cancer and melatonin separately and together would clarify the exact routes in which melatonin affects cancerous cells of the breast.

### 2.1. Apoptosis

Apoptosis is a complicated and sophisticated cellular process by which a metazoan can control the number of its normal and abnormal cells in a programmed manner [23]. Mainly, the process of apoptosis can be triggered by three pathways called granzyme B, intrinsic, and extrinsic [24]. The first pathway is conducted by T cells and natural killer cells through the secretion of a serine protease, granzyme B [25]. The second pathway is dependent to the mitochondria and its alterations and the last pathway is administered by the attachment of some death ligands, like Fas ligand, to their receptor located on the cell surface [26]. After the initiation, all of these three pathways lead to the activation of a class of enzymes called caspases [24,26]. Caspases are a family of cysteine-aspartic proteases which four of them participate in this process and eventually, cause the fragmentation of DNA and destruction of cellular proteins especially the cytoskeleton [23,24]. The regulator factors of this process include some anti-apoptotic and pro-apoptotic genes such as BCL-2, Bax and p53 [27]. Any disturbance in steps of apoptosis can impair the balance between cell survival and death and thus disturbed apoptosis is known for being responsible for many diseases such as cancer [28,29].

In general, apoptosis is one of the cellular mechanisms which melatonin is able to have some effects on its regulation. Melatonin mainly impacts the intrinsic apoptotic pathway by the means of interfering in the mitochondrial function [30,31]. As we know, mitochondria need an electron transport chain or ETC in its inner membrane for the production of ATP [32]. Often, some electrons escape from ETC carriers and produce reactive oxygen species (ROS) by the reduction of oxygen [32]. These free radicals are able to provide a condition in which a lot of damages to the cellular proteins, DNA, carbohydrates, and lipids are caused [33]. This condition is called oxidative stress [33]. Oxidative stress initiates apoptosis by dint of the activation of some signaling pathways such as MAPK/ERK kinases and Hypoxia Inducible Factor [34]. Moreover, mitochondria possess some proteins in its membrane such as second

mitochondria-derived activator or SMAC which can release them to the cytosol and thereby alter the impacts of anti-apoptotic members of Bcl-2 protein family [33,35]. Furthermore, mitochondria are also able to trigger apoptosis by releasing another agent: cytochrome *c* [34]. This agent activates the caspase-3 (this caspase is the final caspase in apoptosis process) via establishing apoptosome [36]. Apoptosome is a complex made up of activating factor-1 or Apaf-1 and pro-caspase-9 which takes part in caspase-9 activation [34].

In general, melatonin impresses apoptosis at the hand of influencing all the mentioned pathways in which mitochondria works [37]. For instance, the antioxidant property of melatonin gives it the power to scavenge free radicals in both direct and indirect manners. indirect route of scavenging occurs through increasing the amounts of glutathione peroxidase subform or GPx4 in mitochondria [38]. As well, discharge of the cytochrome *c*, and antiapoptotic proteins are prone to be affected by melatonin [39]. Furthermore, extrinsic pathway also stands in the scope of impact of melatonin. This happens when melatonin changes Fas and FasL expression and caspase-8 and Bid protein activities [37].

In breast cancer point of view, studies have shown that one of the mechanisms by which melatonin exert its antitumor activities is apoptosis. Noteworthy, melatonin works in two ways in breast cancer cells: caspase-dependent and caspase-independent [40]. Wang and colleagues [41] observed an overexpression in Apaf-1 protein in the melatonin-treated BC cells and concluded that melatonin induces apoptosis by this means. Another study also found that melatonin is able to increase the amounts of p53 protein in MCF-7 cell line but still, more studies are needed in this area [42]. Noshinfar et al. [43] used a combination of melatonin and Arsenic trioxide and revealed that they can affect the expression of three proteins: p53, Bcl-2, and Bax. Besides, melatonin/Arsenic trioxide is able to reduce the activities of hTERT via down-regulating the gene c.Myc. hTERT is a telomerase which is associated with cell proliferation and inhibits the apoptosis mediated by p53 [44]. In another study, researchers utilized melatonin in combination of doxorubicin and observed that they can close some $Ca^{2+}$ channels of the cell membrane and by that, decrease the amounts of $Ca^{2+}$ in the cancerous cell. This event leads to oxidative stress and apoptosis in MCF-7 cells [45]. Gatti et al. [46] produced a melatonin analogue named UCM 1037 and found that this agent is able activate apoptosis in breast cancer cells by affecting caspase-3. El-aziz et al. [47] also reported the same result after the administration of melatonin, retinoic acid and Nigella sativa. Woo et al. [48] worked on MDA-MB-231 cell line and revealed that another way of activating apoptosis by melatonin is augmenting the activities of Bim protein which triggers apoptosis in the presence of tunicamycin. In another trial, the combination of melatonin and all-trans retinoic acid was found to downregulate, upregulate, and upregulate Bcl-2, Bax, and TGF-f1, respectively [49]. In caspase-independent apoptosis view, Cucina and colleagues declared that apoptosis can be triggered by or MDM2/p53 pathway and apoptosis inducing factor or AIF releasing. They also confirmed that in spite of this mechanism, melatonin can initiate apoptosis by altering the expression of TGFβ1 and activating caspases [50].

Murine double minute 2 or MDM2 is an oncogene that encodes MDM2 protein [51]. These proteins bind to p53 and inhibits this protein from functioning [51]. Peroietti et al. [52,53] conducted two studies on melatonin and indicated that this agent is able to decrease the amounts of MDM2 and thereby influence the activity of p53. Hence, they revealed another way for melatonin in increasing apoptosis in breast cancer cells. Gelaleti and other authors also tested the impacts of both melatonin and IL-25 on breast cancer cells and indicated that they can alter the amounts of caspase-3, p53, and p21 [54].

In a recent study by Tran et al., it is shown that melatonin synergistically with doxorubicin induce apoptosis in breast cancer cells via reducting AMP-activated protein kinase α1 (AMPK α1). Noteworthy, it is reported that this reduction is dependant on autophagy [55].

### 2.2. Cell cycle and proliferation

We put the cell cycle tag on a process which any reproducible cell goes through to be divided. This process encompass four phases called G1, S, G2, and M [56]. According to evidence one of the most essential parts of the cancer pathogenesis is cell cycle disturbance [56]. This means that in cancer which is the result of limitless cell proliferation, molecular alterations are affecting key components of this process such as its checkpoints [56]. Disturbed cell cycle is related to a bunch of factors and events such as gene mutations. Two types of mutations exist that are known for altering cell proliferation: the first type mutations mainly create an external mitogen or affect the intracellular signaling pathways that mitogens function through and the second type of mutations are occurring in the G1 checkpoint which is being controlled by pRB. The activity of pRB is also being monitored by some enzymes named Cyclin-dependent kinases or CDKs [57,58]. C-Myc gene is another important component of the proliferation process which its expression manages the entrance of cell to the G1 phase [59]. In addition to some genes, there are also some signaling pathways which are associated with regulating the cell cycle and proliferation. hypoxia-inducible factor-1 or HIF-1 is an agent that increase in response to hypoxia and affects the expression of some cell proliferation-related genes [60]. These genes that are being targeted by HIF-1 include IGF-2 and TGF-a [60]. Another fundamental component of cell proliferation is the pathway of PI3K/Akt/mTOR. In this complicated pathway, at first, Phosphoinositide 3-kinases or PI3K activates protein kinase B or Akt by the means of phosphorylation and then this kinase impacts a bunch of downstream agents that alter the expression of cell proliferation-related genes [61].

Cell cycle and proliferation is one of the engaged factors in the pathogenesis of breast cancer. Accumulative evidence demonstrates that inhibiting checkpoints of the cell cycle in cancerous cells of the breast is a result of binding estrogen to its receptors on these cells. This event alters the expression of some genes such as Cyclin D1 and thereby, restricts the cell cycle [62]. One of the studies that investigated the role of melatonin in cell proliferation of BC cells has showed that melatonin is able to increase the expression of both p53 and p21 proteins. Therefore, p53/p21 pathway is the way melatonin affects cell cycle [42]. Noshinfar et al. [43] combined melatonin with Arsenic trioxide and used it on MCF-7 cell line and found that this combination is able to increase p53 expression and thus, affect cell proliferation through the p53/p21 pathway. Furthermore, this combination decreases the expression of hTERT which has a role in cell immortality and oncogenesis [44].

Cos et al. [63] also studied the impacts of melatonin on MCF-7 cells and expressed that melatonin is able to prolong the G0/G1 duration and hence, decreases the cell proliferation rate. As well, in two other studies, Cos et al. [64,65] affirmed the impact of melatonin against the proliferation of breast cancer cells. Jawed et al. [66] established a mixture of melatonin and valproic acid and found that valproic acid helps expressing the MT1 receptor and hence, utilizing both of this agents together will have a stronger anti-proliferative effect on breast cancer cells. Lai and colleagues looked into another combination: melatonin, all-trans retinoic acid, and somatostatin. In another trial the anti-proliferative function of melatonin was attributed to two types of G-protein: Gαi2 and Gαq proteins [67]. On the subject of HIF-1, Cheng et al. [68] declared that melatonin suppresses this agent but they did not mentioned HIF-1

specifically for anti-proliferative effects and therefore, further investigations are needed.

### 2.3. Inflammation

Inflammation is acknowledged as an elaborated mechanism by which any tissue injury can be repaired [69]. In this series of actions, leukocytes including macrophages, neutrophils, and dendritic cells are being activated and conducted towards the site of injury [69]. Along with these cells, some cytokines and cytotoxic mediators which are secreted from the activated immune cells modulate the inflammation response: ROS, serine and cysteine proteases, matrix metalloproteinases or MMPs, TNF-α, interleukins, and interferons [70]. Currently, inflammation has achieved a position in the initiation of a cancer; but how is this possible? The answer of this question lies in the concept of the production of free radicals such as ROS by inflammatory cells in order to destroy the infected cells. Therefore, cancer production is one of the side effects of the DNA mutations following the ROS release [69].

In the molecular point of view, after the secretion of some agents in the inflammation site, some intracellular signaling pathways are triggered [71,72]. One of these pathways that its activation has been frequently observed in diverse cancers is NF-κB signaling pathway [71]. The NF-κB signaling pathway activates after the cell exposure with some factors such as ROS, CD14, and TNF-α [73]. This pathway which is mediated by toll-like receptors is able to help the initiation and progression of many kinds of cancer [71,72].

The anti-inflammatory role of melatonin is investigated many types of cancer including breast cancer. Woo and two others revealed that melatonin reduces the COX-2 expression in MDA-MB-231 cells [48]. As well, Wang et al. [41] observed that melatonin inhibited COX-2 and NF-κB signaling pathways. They added that p300 down-regulation is making the regulation of NF-κB pathway possible by melatonin. Colombo et al. [74] also identified the role of melatonin in decreasing the NF-κB expression. Another group of researchers examined the cytokine concentration in MCF-7 cells after melatonin addition and found that TNF-α, IL-6, and IL-11 are decreased in the presence of melatonin [75]. In another paper, it is acknowledged that melatonin affects cytokine and COX-1, 2 expression and therefore it is a proper candidate for modulating the impacts of chemo and radiotherapy in breast cancer cells [76].

### 2.4. Other mechanisms

Beside the mentioned mechanisms, there are also some other mechanisms that the role of melatonin on them in breast cancer is not well-considered. These mechanisms include angiogenesis, attachment of estrogen into its receptor, and the interaction between melatonin and calmodulin.

#### 2.4.1. Angiogenesis

Angiogenesis is another essential mechanism for the cancer progression which is defined as “production of new vessels from the pre-existing blood vessels”. This event occurs when HIF-1 migrates to the nucleus in response to hypoxia [77]. HIF-1 migration leads to the activation some factors such as VEGF-A or Vascular endothelial growth factor, platelet-derived growth factor or PDGF, and epidermal growth factor (EGF) [77,78]. The augmentation in the levels of these agents results in the translocation of some cells such as endothelial progenitor cells or EPCs which are the main cellular component of producing new vessels [77]. As Shirakawa and colleagues reported that the number of EPCs and amounts of VEGF are significantly increased in breast cancer [79]. On the other hand, melatonin is also confirmed to affect angiogenesis by the means of impacting VEGF and HIF-1 [80–83]. As a matter of fact, there are not many investigations on the subject of anti-angiogenic properties of melatonin in breast cancer. Nevertheless, a group of scientists observed considerably decreased levels of VEGF receptor in mice treated with melatonin [84]. Talib and Saleh [85] also examined a combination of melatonin and a bacteria named Propionibacterium acnes on mice and declared that this mixture can reduce angiogenesis in breast cancer patients.

#### 2.4.2. Estrogen and estrogen receptor

As mentioned before, estrogen and estrogen receptors have a crucial part in breast cancer so that the types of this cancer are defined by the presence or absence of estrogen receptors. Estrogen receptor-alpha signaling pathways are involved in growth and differentiation of BC cells. Noteworthy, these receptors are showing anti-apoptotic activities of themselves [86]. Molis et al. conducted an *in vitro* study and demonstrated that melatonin impacts the regulation of estrogen receptor gene and thereby inhibits the MCF-7 cells from proliferating [87]. Putting the impacts of melatonin on estrogen receptors aside, it also is able to affect the extent of estrogen itself. In a study the effects of melatonin on aromatase which is responsible for the production of estrogen in breast cancer cells was considered. As they concluded “melatonin decreases the aromatase activity and expression. Lower levels of aromatase lead to lower levels of estrogens, resulting in decreased growth and development of breast tumors” [88].

#### 2.4.3. $Ca^{2++}$ and calmodulin regulation

One of the ways by which melatonin is able to affect the growth of cancerous cells is altering the intracellular concentration of $Ca^{2+}$. The exact mechanisms by which melatonin does this duty is not clear but some evidence represent the concept of an intracellular protein called calmodulin or CaM [89]. This protein mediates the $Ca^{2+}$ signaling pathways and by that route affects some essential cellular mechanisms such as cell cycle [90]. In breast cancer, Dai et al. [91] are the only ones who considered roles of melatonin in MCF-7 cells in this way. They expressed that melatonin affects CaM-related pathways and cell-cell adhesion in a positive way and augments [Ca2+]i and therefore, takes part in reducing invasion of breast cancer cells.

#### 2.4.4. Non-coding RNAs

Non-coding RNAs (e.g. micro RNAs (miRNAs) and long non coding RNAs (lncRNAs)) have recently attracted a lot of attention in the field of cancer treatment [92]. Therefore, we review the literature concerning with the role of melatonin in affecting non-coding RNAs in breast cancer. However, these studies are limited and more investigations are needed to find the exact role of non-coding RNAs in melatonin anti-breast cancer roles.

A study has shown that lnc010561 and FK506-binding protein 3 (FKBP3) levels are reduced in breast cancer cells treated with melatonin. While the downregulation of LNC010561 and FKBP3 leads to the supression of proliferation and invasion, it can induce apoptosis in cancer cells. Furthermore, they also work as competing endogenous RNAs for miR-30. Therefore, it is suggested that melatonin may inhibit the progression of breast cancer through FKBP3/LNC010561/miR-30 axis [93]. Another similar study has reported that following melatonin treatment, LNC049808 and FUNDC1 are decreased in tirple-negative breast cancer cells. Furthermore, LNC049808 and FUNDC1 functions as competeing engogenous RNAs for miR-101 [94]. In triple-negative breast cancer cells, melatonin is reported to decrease migration and proliferation. Taqman assays have demonstrated that in melatonin-treated cells, 11 miRNAs are upregulated while 6 miRNAs are downregulated. Two of these miRNAs are miR-148b, an anti-metastatic miRNA, and

miR-210, an oncogenic miRNA. Both of these miRNAs are reported to be upregulated following melatonin treatment. However, depletion of these miRNAs in breast cancer cells does not affect melatonin's effect on migration [95]. In MDA-MB-468 breast cancer cells, melatonin is shown both *in vitro* and *in vivo* to enhance miR-152-3p gene expression as well as its target gene while decreasing the protein of the genes [96].

## 3. Clinical trials

Lissoni and colleagues tried melatonin in combination with chemotherapy on 77 metastatic breast cancer patients for examining its effects on increasing the efficacy of chemotherapy [97]. They treated a group of patients with either mitoxantrone, doxorubicin or paclitaxel and another group with the combination melatonin (20 mg/day orally every day) and chemotherapeutic drugs [97]. They found that melatonin is able to increase the rate of both tumor regression and 1-year survival when used in combination with a chemotherapeutic drug. However, these results are not specific to breast cancer because in this study some other solid tumors were examined, as well [97]. In another study, Lissoni et al. [98] compared the administration of Tamoxifen alone with the combination of tamoxifen and melatonin. They entered 14 metastatic breast cancer patients in this pilot phase II study and concluded that using 20 mg of melatonin everyday starting 7 days before tamoxifen treatment is useful for inducing the objective tumour regression [98]. Despites these studies, it seems that melatonin alone is not as effective as in combination with other drugs. A study on 95 postmenopausal women with a history of breast cancer (stages 0-III) showed that breast cancer biomarkers like estradiol and insulin-like growth factor I (IGF-1) are not decreased after four months of 3 mg daily treatment of melatonin [99]. Furthermore, studies also has shown that melatonin is beneficial for decreasing the toxicity and side effects of chemotherapeutic drugs including thrombocytopenia [97,100], sleep [101,102], depressive symptoms [101,103], fatigue [104], and anxiety [103].

## 4. Concluding remarks

Despite all the improvements in the fields of cancer prognosis, diagnosis, and treatment, still, a large number of gaps can be found that are making cancer one of the leading causes of death, worldwide. Among all cancers, statistics show that breast cancer stands in the second position, after lung cancer, among all common cancers in men and women. Furthermore, this cancer is acknowledged to be the most frequent cancer between women and 2,088,849 new cases were diagnosed of this cancer in 2018 [105]. In regard to the poor prognosis and high mortality rate, this cancer has drowned the attention of a large body of research in order to enhance the status of breast cancer patients. Recently, melatonin has approved to be an efficient therapeutic agent because of its potentials in regulating and affecting many cellular and molecular means such as apoptosis, cell proliferation, inflammation, and angiogenesis. In this paper, we tried to create a bridge between the factors involved in breast cancer pathogenesis and the mechanisms affected by melatonin in order to reveal the exact routs by which melatonin inhibits BC progression (Tables 1–4 and Fig. 1). We conclude that melatonin has the potential to be used in breast cancer treatment

**Table 1**
Empirical studies investigating the role of melatonin on apoptosis of BC.

| Authors | Model | Function | References |
|---|---|---|---|
| Wang et al. | *In vitro* | Overexpression of Apaf-1 protein | [41] |
| Cos et al. | *In vitro* | Augmentation the amounts of p53 protein | [42] |
| Noshinfar et al. | *In vitro* | Combination of melatonin and Arsenic trioxide can affect the expression of p53, Bcl-2, and Bax. Reducing the activities of hTERT via down-regulating the gene c-Myc | [43] |
| Kosar et al. | *In vitro* | Combination of doxorubicin and melatonin increases oxidative stress by elevating $Ca^{2+}$ amounts | [45] |
| Gatti et al. | *In vitro* | Melatonin analogue or UCM 1037 activates caspase-3 | [46] |
| El-aziz et al. | *In vivo* | Administration of melatonin, retinoic acid and Nigella sativa activates caspase-3 | [47] |
| Woo et al. | *In vitro* | Augmenting the activities of Bim protein which triggers apoptosis in the presence of tunicamycin. | [48] |
| Eck-Enriquez et al. | *In vitro* | combination of melatonin and all-trans retinoic acid downregulates Bcl-2 and upregulates Bax and TGF-f1 | [49] |
| Cucina et al. | *In vitro* | Affecting MDM2/p53 pathway and apoptosis inducing factor or AIF releasing, affecting the expression of TGFβ1 and caspases | [50] |
| Peroietti et al. | *In vitro* | Decreasing the amounts of MDM2 and thereby influence the activity of p53 | [52,53] |
| Gelaleti et al. | *In vitro* | melatonin and IL-25 can alter the amounts of caspase-3, p53, and p21 | [54] |

**Table 2**
Experimental studies on melatonin effects on cell cycle and proliferation.

| Authors | Model | Function | References |
|---|---|---|---|
| Cos et al. | *In vitro* | increase the expression of both p53 and p21 proteins | [42] |
| Noshinfar et al. | *In vitro* | Melatonin with Arsenic trioxide together increase p53 expression and thus, affect cell proliferation through the p53/p21 pathway and downregulation of hTERT | [43] |
| Cos et al. | *In vitro* | Prolonging the G0/G1 duration and hence, decreasing the cell proliferation rate | [63–65] |
| Jawed et al. | *In vitro* | Mixture of melatonin and valproic acid reduce proliferation in cancer cells | [66] |
| Lai et al. | *In vitro* | Melatonin affects proliferation through two types of G-protein: Gαi2 and Gαq proteins | [67] |
| Cheng et al. | *In vitro* | Suppressing HIF-1 | [68] |

**Table 3**
Empirical studies conducted on the anti-inflammatory role of melatonin in breast cancer.

| Authors | Model | Function | References |
|---|---|---|---|
| Woo et al. | *In vitro* | Reduction of the COX-2 expression | [48] |
| Wang et al. | *In vitro* | Inhibition of COX-2 and NF-κB signaling pathways byt p300 down-regulation | [41] |
| Colombo et al. | *In vitro* | Decreasing the NF-κB expression | [74] |
| Alvarez-Garcia et al. | *In vitro* | Decreasing the levels of TNF-α, IL-6, and IL-11 | [88] |
| Gonzalez-Gonzalez et al. | *In vitro* | Affecting cytokine and COX-1,2 expression and modulating the impacts of chemo and radiotherapy | [76] |

**Table 4**
Experimental studies on melatonin effects on angiogenesis, calmodulin, and estrogen and its receptors.

| Effect | Authors | Model | Function | References |
|---|---|---|---|---|
| Angiogenesis | Jardim-Perassi et al. | *In vivo* | Decreasing levels of VEGF receptor | [84] |
| | Talib and Saleh | *In vivo* | Combination of melatonin and Propionibacterium acnes reduces angiogenesis | [85] |
| Estrogen and its receptors | Molis et al. | *In vitro* | Impacting the regulation of estrogen receptor gene | [87] |
| | Alvarez-García et al. | *In vitro* | Decreasing the aromatase activity and expression and lowering estrogen extents | [88] |
| $Ca^{2+}$ and calmodulin interaction | Dai et al. | *In vitro* | Affecting CaM-related pathways and cell-cell adhesion in and augmenting [Ca2+]i | [91] |

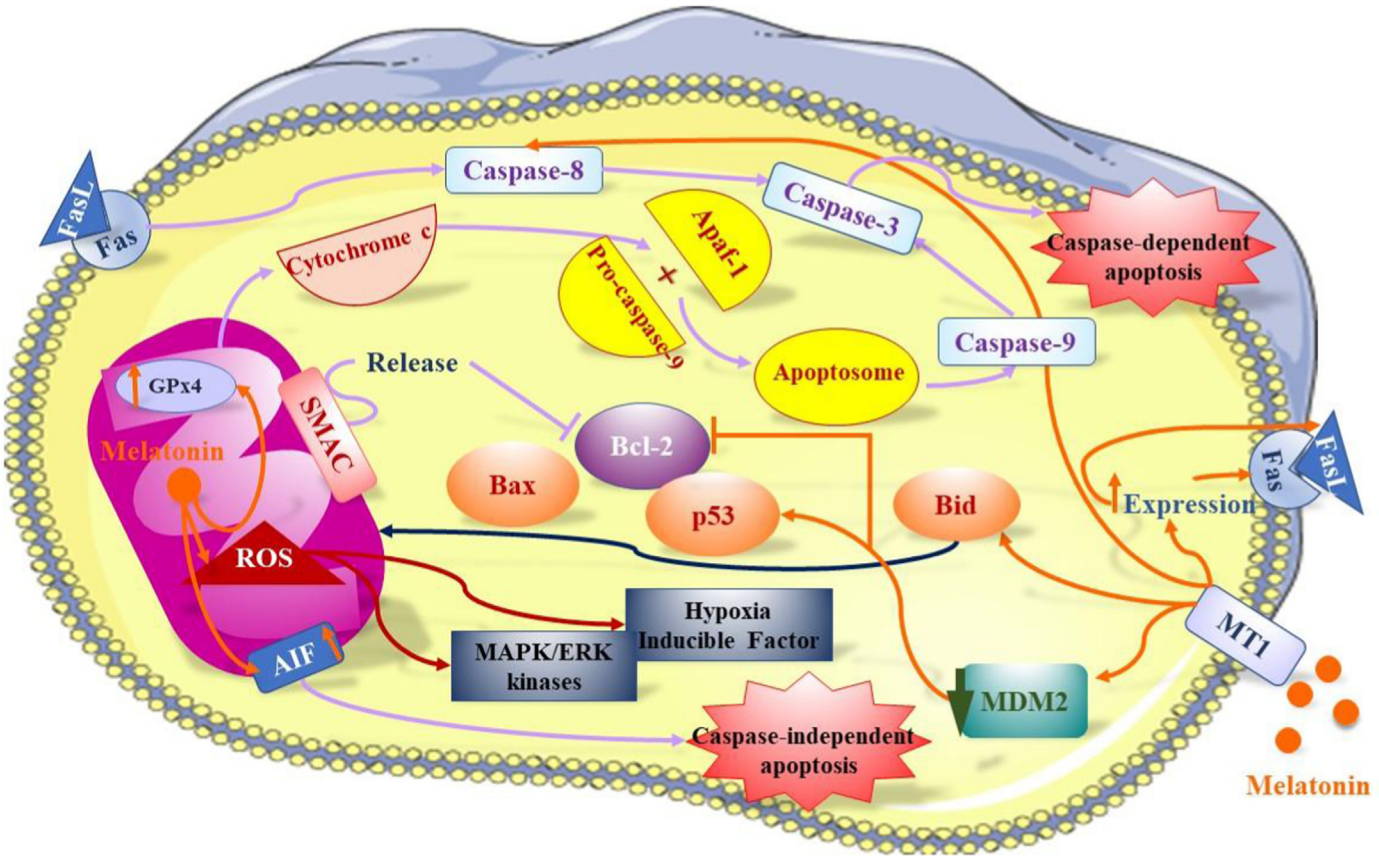


**Fig. 1.** Schematic presentation of melatonin roles in breast cancer.

alone or adjuvant to chemo and radiotherapy in order to modulate their side effects. Due to the availability of this compound and easy consumption, it is not unreasonable to expect that melatonin becomes one of the most common therapies for breast cancer patients in the future. Overall, melatonin and its roles in augmenting apoptosis and reducing inflammation, angiogenesis, and cell proliferation are giving a novel insight to the scientific community and BC patients for a more efficient treatment. However, most of studies working on this subject are carried out on breast cancer cell lines, and that's why this information is insufficient to decipher the complexity of action of melatonin, especially since it is an important regulator of the circadian rhythm. Furthermore, the number of studies examining melatonin alone is notably fewer than studies which has used melatonin in combination with another agent or a chemotherapeutic drug and that makes it hard to dissociate the direct and indirect effects of melatonin on cancer cells; thus we suggest that using models of spontaneous or induced tumorigenesis would help solving this problem.

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## Author contributions

F.Sadoughi, P.Maleki Dana, Z.Asemi, R.Shafabakhash, S.Mohammadi, N.Targhazeh and H.Mirzaei contributed in conception, design and drafting of the manuscript.

Z.Heidar and M.Mirzamoradi critically contributed in the revised version.

All authors approved the final version for submission.

## Ethics approval and consent to participate

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The authors declare no conflict of interest.

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## References

[1] A.M. Filadelfi, A.M. Castrucci, Comparative aspects of the pineal/melatonin system of poikilothermic vertebrates, J. Pineal Res. 20 (4) (1996) 175–186.
[2] R. Jockers, P. Delagrange, M.L. Dubocovich, R.P. Markus, N. Renault, G. Tosini, et al., Update on melatonin receptors: IUPHAR Review 20, Br. J. Pharmacol. 173 (18) (2016) 2702–2725.
[3] J. Barrenetxe, P. Delagrange, J. Martinez, Physiological and metabolic functions of melatonin, J. Physiol. Biochem. 60 (1) (2004) 61–72.
[4] P. Klosen, S. Lapmanee, C. Schuster, B. Guardiola, D. Hicks, P. Pevet, et al., MT1 and MT2 melatonin receptors are expressed in nonoverlapping neuronal populations, J. Pineal Res. 67 (1) (2019), e12575.
[5] S.G. Grant, M.A. Melan, J.J. Latimer, P.A. Witt-Enderby, Melatonin and breast cancer: cellular mechanisms, clinical studies and future perspectives, Expet Rev. Mol. Med. 11 (2009) e5.
[6] L. Brydon, F. Roka, L. Petit, P. de Coppet, M. Tissot, P. Barrett, et al., Dual signaling of human Mel1a melatonin receptors via G(i2), G(i3), and G(q/11) proteins, Mol. Endocrinol. 13 (12) (1999) 2025–2038.
[7] N.M. Radio, J.S. Doctor, P.A. Witt-Enderby, Melatonin enhances alkaline phosphatase activity in differentiating human adult mesenchymal stem cells grown in osteogenic medium via MT2 melatonin receptors and the MEK/ERK (1/2) signaling cascade, J. Pineal Res. 40 (4) (2006) 332–342.
[8] P.M. Dana, F. Sadoughi, M. Mobini, R. Shafabakhsh, S. Chaichian, B. Moazzami, et al., Molecular and biological functions of melatonin in endometrial cancer, Curr. Drug Targets 21 (5) (2020) 519–526.
[9] H. Fathizadeh, H. Mirzaei, Z. Asemi, Melatonin: an anti-tumor agent for osteosarcoma, Cancer Cell Int. 19 (2019) 319.
[10] M. Maleki, N. Khelghati, F. Alemi, S. Younesi, Z. Asemi, R. Abolhasan, et al., Multiple interactions between melatonin and non-coding RNAs in cancer biology, Chem. Biol. Drug Des. 98 (3) (2021) 323–340.
[11] R. Shafabakhsh, H. Mirzaei, Z. Asemi, Melatonin: a promising agent targeting leukemia, J. Cell. Biochem. 121 (4) (2020) 2730–2738.
[12] E.A. Rakha, A.R. Green, Molecular classification of breast cancer: what the pathologist needs to know, Pathology 49 (2) (2017) 111–119.
[13] E.A. Rakha, J.S. Reis-Filho, F. Baehner, D.J. Dabbs, T. Decker, V. Eusebi, et al., Breast cancer prognostic classification in the molecular era: the role of histological grade, Breast Cancer Res. 12 (4) (2010) 207.
[14] B. Weigelt, J.S. Reis-Filho, Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat. Rev. Clin. Oncol. 6 (12) (2009) 718–730.
[15] B. Weigelt, F.C. Geyer, J.S. Reis-Filho, Histological types of breast cancer: how special are they? Mol. Oncol. 4 (3) (2010) 192–208.
[16] U. Veronesi, P. Boyle, A. Goldhirsch, R. Orecchia, G. Viale, Breast cancer, Lancet 365 (9472) (2005) 1727–1741.
[17] S. Winters, C. Martin, D. Murphy, N.K. Shokar, Breast cancer epidemiology, prevention, and screening, Prog. Mol. Biol. Transl. Sci. 151 (2017) 1–32.
[18] S. Mittal, H. Kaur, N. Gautam, A.K. Mantha, Biosensors for breast cancer diagnosis: a review of bioreceptors, biotransducers and signal amplification strategies, Biosens. Bioelectron. 88 (2017) 217–231.
[19] A.M. Chiarelli, M.V. Prummel, D. Muradali, V. Majpruz, M. Horgan, J.C. Carroll, et al., Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program, J. Clin. Oncol. 32 (21) (2014) 2224–2230.
[20] S.H. Jafari, Z. Saadatpour, A. Salmaninejad, F. Momeni, M. Mokhtari, J.S. Nahand, et al., Breast cancer diagnosis: imaging techniques and biochemical markers, J. Cell. Physiol. 233 (7) (2018) 5200–5213.
[21] C.R. Graveel, H.M. Calderone, J.J. Westerhuis, M.E. Winn, L.F. Sempere, Critical analysis of the potential for microRNA biomarkers in breast cancer management, Breast Cancer 7 (2015) 59–79.
[22] M.B. Suter, O. Pagani, Should age impact breast cancer management in young women? Fine tuning of treatment guidelines, Ther. Adv. Med. Oncol. 10 (2018), 1758835918776923.
[23] M.O. Hengartner, The biochemistry of apoptosis, Nature 407 (6805) (2000) 770–776.
[24] S. Elmore, Apoptosis: a review of programmed cell death, Toxicol. Pathol. 35 (4) (2007) 495–516.
[25] I.S. Afonina, S.P. Cullen, S.J. Martin, Cytotoxic and non-cytotoxic roles of the CTL/NK protease granzyme B, Immunol. Rev. 235 (1) (2010) 105–116.
[26] M.S. D'Arcy, Cell death: a review of the major forms of apoptosis, necrosis and autophagy, Cell Biol. Int. 43 (6) (2019) 582–592.
[27] J.M. Hardwick, L. Soane, Multiple functions of BCL-2 family proteins, Cold Spring Harbor Perspect. Biol. 5 (2) (2013).
[28] M. Hassan, H. Watari, A. AbuAlmaaty, Y. Ohba, N. Sakuragi, Apoptosis and molecular targeting therapy in cancer, BioMed Res. Int. 2014 (2014) 150845.
[29] G. Pistritto, D. Trisciuoglio, C. Ceci, A. Garufi, G. D'Orazi, Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies, Aging (N Y) 8 (4) (2016) 603–619.
[30] H. Zare, R. Shafabakhsh, R.J. Reiter, Z. Asemi, Melatonin is a potential inhibitor of ovarian cancer: molecular aspects, J. Ovarian Res. 12 (1) (2019) 26.
[31] S. Qiu, Z.B. Tao, L. Tao, Y. Zhu, Melatonin induces mitochondrial apoptosis in osteoblasts by regulating the STIM1/cytosolic calcium elevation/ERK pathway, Life Sci. 248 (2020), 117455.
[32] L.B. Sullivan, N.S. Chandel, Mitochondrial reactive oxygen species and cancer, Cancer Metabol. 2 (1) (2014) 17.
[33] L.G. de Almeida Chuffa, F.R.F. Seiva, M.S. Cucielo, H.S. Silveira, R.J. Reiter, L.A. Lupi, Mitochondrial functions and melatonin: a tour of the reproductive cancers, Cell. Mol. Life Sci. 76 (5) (2019) 837–863.
[34] S. Proietti, A. Cucina, M. Minini, M. Bizzarri, Melatonin, mitochondria, and the cancer cell, Cell. Mol. Life Sci. 74 (21) (2017) 4015–4025.
[35] L.M. Dejean, S. Martinez-Caballero, S. Manon, K.W. Kinnally, Regulation of the mitochondrial apoptosis-induced channel, MAC, by BCL-2 family proteins, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1762 (2) (2006) 191–201.
[36] R. Sainz, J. Mayo, C. Rodriguez, D. Tan, S. Lopez-Burillo, R.J. Reiter, Melatonin and cell death: differential actions on apoptosis in normal and cancer cells, Cell. Mol. Life Sci. CMLS 60 (7) (2003) 1407–1426.
[37] M. Bizzarri, S. Proietti, A. Cucina, R.J. Reiter, Molecular mechanisms of the pro-apoptotic actions of melatonin in cancer: a review, Expert Opin. Ther. Targets 17 (12) (2013) 1483–1496.
[38] R. Hardeland, Melatonin and the electron transport chain, Cell. Mol. Life Sci. 74 (21) (2017) 3883–3896.
[39] 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. 61 (3) (2016) 253–278.
[40] S. Proietti, A. Cucina, R.J. Reiter, M. Bizzarri, Molecular mechanisms of melatonin's inhibitory actions on breast cancers, Cell. Mol. Life Sci. 70 (12) (2013) 2139–2157.
[41] J. Wang, X. Xiao, Y. Zhang, D. Shi, W. Chen, L. Fu, et al., 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 (1) (2012) 77–90.
[42] S. Cos, M.D. Mediavilla, R. Fernandez, D. Gonzalez-Lamuno, E.J. Sanchez-Barcelo, Does melatonin induce apoptosis in MCF-7 human breast cancer cells in vitro? J. Pineal Res. 32 (2) (2002) 90–96.
[43] E. Nooshinfar, D. Bashash, A. Safaroghli-Azar, S. Bayati, M. Rezaei-Tavirani, S.H. Ghaffari, et al., Melatonin promotes ATO-induced apoptosis in MCF-7 cells: proposing novel therapeutic potential for breast cancer, Biomed. Pharmacother. 83 (2016) 456–465.
[44] T. Kanaya, S. Kyo, K. Hamada, M. Takakura, Y. Kitagawa, H. Harada, et al., Adenoviral expression of p53 represses telomerase activity through down-regulation of human telomerase reverse transcriptase transcription, Clin. Cancer Res. 6 (4) (2000) 1239–1247.
[45] P.A. Kosar, M. Naziroglu, I.S. Ovey, B. Cig, 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 (1–2) (2016) 129–140.
[46] G. Gatti, V. Lucini, S. Dugnani, A. Calastretti, G. Spadoni, A. Bedini, et al., Antiproliferative and pro-apoptotic activity of melatonin analogues on melanoma and breast cancer cells, Oncotarget 8 (40) (2017) 68338–68353.
[47] M.A.A. El-Aziz, H.A. Hassan, M.H. Mohamed, A.R.M. Meki, S.K. Abdel-Ghaffar, M.R. Hussein, The biochemical and morphological alterations following administration of melatonin, retinoic acid and Nigella sativa in mammary carcinoma: an animal model, Int. J. Exp. Pathol. 86 (6) (2005) 383–396.
[48] 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 (3) (2015) 310–320.
[49] K. Eck-Enriquez, T.L. Kiefer, L.L. Spriggs, S.M. Hill, Pathways through which a regimen of melatonin and retinoic acid induces apoptosis in MCF-7 human breast cancer cells, Breast Cancer Res. Treat. 61 (3) (2000) 229–239.
[50] A. Cucina, S. Proietti, F. D'Anselmi, P. Coluccia, S. Dinicola, L. Frati, et al., Evidence for a biphasic apoptotic pathway induced by melatonin in MCF-7 breast cancer cells, J. Pineal Res. 46 (2) (2009) 172–180.
[51] J. Momand, H.-H. Wu, G. Dasgupta, MDM2—master regulator of the p53 tumor suppressor protein, Gene 242 (1–2) (2000) 15–29.
[52] S. Proietti, A. Cucina, F. D'Anselmi, S. Dinicola, A. Pasqualato, E. Lisi, et al., Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFbeta-1-dependent growth inhibition of breast cancer cells, J. Pineal Res. 50 (2) (2011) 150–158.
[53] S. Proietti, A. Cucina, G. Dobrowolny, F. D'Anselmi, S. Dinicola, M.G. Masiello, et al., Melatonin down-regulates MDM2 gene expression and enhances p53 acetylation in MCF-7 cells, J. Pineal Res. 57 (1) (2014) 120–129.
[54] G.B. Gelaleti, T.F. Borin, L.B. Maschio-Signorini, M.G. Moschetta, B.V. Jardim-Perassi, G.B. Calvinho, et al., Efficacy of melatonin, IL-25 and siIL-17B in tumorigenesis-associated properties of breast cancer cell lines, Life Sci. 183 (2017) 98–109.
[55] Q.H. Tran, D.H. Hoang, M. Song, W. Choe, I. Kang, S.S. Kim, et al., Melatonin and doxorubicin synergistically enhance apoptosis via autophagy-dependent reduction of AMPKα1 transcription in human breast cancer cells, Exp. Mol.

Med. 53 (9) (2021) 1413–1422.
[56] K.L. Thu, I. Soria-Bretones, T.W. Mak, D.W. Cescon, Targeting the cell cycle in breast cancer: towards the next phase, Cell Cycle 17 (15) (2018) 1871–1885.
[57] G.I. Evan, K.H. Vousden, Proliferation, cell cycle and apoptosis in cancer, Nature 411 (6835) (2001) 342–348.
[58] M. Malumbres, Cyclin-dependent kinases, Genome Biol. 15 (6) (2014) 122.
[59] S. Pelengaris, M. Khan, G. Evan, c-MYC: more than just a matter of life and death, Nat. Rev. Cancer 2 (10) (2002) 764–776.
[60] Q. Ke, M. Costa, Hypoxia-inducible factor-1 (HIF-1), Mol. Pharmacol. 70 (5) (2006) 1469–1480.
[61] J.A. Engelman, J. Luo, L.C. Cantley, The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism, Nat. Rev. Genet. 7 (8) (2006) 606–619.
[62] N. Platet, A.M. Cathiard, M. Gleizes, M. Garcia, Estrogens and their receptors in breast cancer progression: a dual role in cancer proliferation and invasion, Crit. Rev. Oncol. Hematol. 51 (1) (2004) 55–67.
[63] S. Cos, J. Recio, E. Sánchez-Barceló, Modulation of the length of the cell cycle time of MCF-7 human breast cancer cells by melatonin, Life Sci. 58 (9) (1996) 811–816.
[64] S. Cos, E.J. Sanchez-Barcelo, Differences between pulsatile or continuous exposure to melatonin on MCF-7 human breast cancer cell proliferation, Cancer Lett. 85 (1) (1994) 105–109.
[65] S. Cos, E.J. Sanchez-Barcelo, Melatonin inhibition of MCF-7 human breast-cancer cells growth: influence of cell proliferation rate, Cancer Lett. 93 (2) (1995) 207–212.
[66] S. Jawed, B. Kim, T. Ottenhof, G.M. Brown, E.S. Werstiuk, L.P. Niles, Human melatonin MT1 receptor induction by valproic acid and its effects in combination with melatonin on MCF-7 breast cancer cell proliferation, Eur. J. Pharmacol. 560 (1) (2007) 17–22.
[67] L. Lai, L. Yuan, Q. Chen, C. Dong, L. Mao, B. Rowan, et al., The Galphai and Galphaq proteins mediate the effects of melatonin on steroid/thyroid hormone receptor transcriptional activity and breast cancer cell proliferation, J. Pineal Res. 45 (4) (2008) 476–488.
[68] J. Cheng, H.L. Yang, C.J. Gu, Y.K. Liu, J. Shao, R. Zhu, et al., Melatonin restricts the viability and angiogenesis of vascular endothelial cells by suppressing HIF-1alpha/ROS/VEGF, Int. J. Mol. Med. 43 (2) (2019) 945–955.
[69] L.M. Coussens, Z. Werb, Inflammation and cancer, Nature 420 (6917) (2002) 860–867.
[70] E. Feiken, J. Romer, J. Eriksen, L.R. Lund, Neutrophils express tumor necrosis factor-alpha during mouse skin wound healing, J. Invest. Dermatol. 105 (1) (1995) 120–123.
[71] B. Hoesel, J.A. Schmid, The complexity of NF-kappaB signaling in inflammation and cancer, Mol. Cancer 12 (2013) 86.
[72] K. Newton, V.M. Dixit, Signaling in innate immunity and inflammation, Cold Spring Harbor Perspect. Biol. 4 (3) (2012).
[73] N.S. Chandel, W.C. Trzyna, D.S. McClintock, P.T. Schumacker, Role of oxidants in NF-κB activation and TNF-α gene transcription induced by hypoxia and endotoxin, J. Immunol. 165 (2) (2000) 1013–1021.
[74] J. Colombo, B.V. Jardim-Perassi, J.P.S. Ferreira, C.Z. Braga, N.M. Sonehara, R.P. Junior, et al., Melatonin differentially modulates NF-small ka, CyrillicB expression in breast and liver cancer cells, Anti Cancer Agents Med. Chem. 18 (12) (2018) 1688–1694.
[75] V. Alvarez-Garcia, A. Gonzalez, C. Alonso-Gonzalez, C. Martinez-Campa, S. Cos, Melatonin interferes in the desmoplastic reaction in breast cancer by regulating cytokine production, J. Pineal Res. 52 (3) (2012) 282–290.
[76] A. Gonzalez-Gonzalez, E. Garcia Nieto, A. Gonzalez, C. Sanchez-Fernandez, C. Alonso-Gonzalez, J. Menendez-Menendez, et al., Melatonin modulation of radiation and chemotherapeutics-induced changes on differentiation of breast fibroblasts, Int. J. Mol. Sci. 20 (16) (2019).
[77] Z. Zhou, H. Yao, H. Hu, Disrupting tumor angiogenesis and "the hunger games" for breast cancer, Adv. Exp. Med. Biol. 1026 (2017) 171–195.
[78] W.H. Talib, Melatonin and cancer hallmarks, Molecules 23 (3) (2018).
[79] K. Shirakawa, S. Furuhata, I. Watanabe, H. Hayase, A. Shimizu, Y. Ikarashi, et al., Induction of vasculogenesis in breast cancer models, Br. J. Cancer 87 (12) (2002) 1454–1461.
[80] Y. Zhang, Q. Liu, F. Wang, E.A. Ling, S. Liu, L. Wang, et al., Melatonin antagonizes hypoxia-mediated glioblastoma cell migration and invasion via inhibition of HIF-1alpha, J. Pineal Res. 55 (2) (2013) 121–130.
[81] A.B. Cerezo, R. Hornedo-Ortega, M.A. Alvarez-Fernandez, A.M. Troncoso, M.C. Garcia-Parrilla, Inhibition of VEGF-induced VEGFR-2 activation and HUVEC migration by melatonin and other bioactive indolic compounds, Nutrients 9 (3) (2017).
[82] P. Lissoni, F. Rovelli, F. Malugani, R. Bucovec, A. Conti, G.J. Maestroni, Anti-angiogenic activity of melatonin in advanced cancer patients, Neuroendocrinol. Lett. 22 (1) (2001) 45–47.
[83] D. Lv, P.L. Cui, S.W. Yao, Y.Q. Xu, Z.X. Yang, Melatonin inhibits the expression of vascular endothelial growth factor in pancreatic cancer cells, Chin. J. Cancer Res. 24 (4) (2012) 310–316.
[84] B.V. Jardim-Perassi, A.S. Arbab, L.C. Ferreira, T.F. Borin, N.R. Varma, A.S. Iskander, et al., Effect of melatonin on tumor growth and angiogenesis in xenograft model of breast cancer, PLoS One 9 (1) (2014), e85311.
[85] W.H. Talib, S. Saleh, Propionibacterium acnes augments antitumor, anti-angiogenesis and immunomodulatory effects of melatonin on breast cancer implanted in mice, PLoS One 10 (4) (2015), e0124384.
[86] A.M. Band, M. Laiho, Crosstalk of TGF-β and estrogen receptor signaling in breast cancer, J. Mammary Gland Biol. Neoplasia 16 (2) (2011) 109–115.
[87] T.M. Molis, L.L. Spriggs, S.M. Hill, Modulation of estrogen receptor mRNA expression by melatonin in MCF-7 human breast cancer cells, Mol. Endocrinol. 8 (12) (1994) 1681–1690.
[88] V. Alvarez-García, A. González, C. Alonso-González, C. Martínez-Campa, S. Cos, Melatonin interferes in the desmoplastic reaction in breast cancer by regulating cytokine production, J. Pineal Res. 52 (3) (2012) 282–290.
[89] G. Benítez-King, L. Huerto-Delgadillo, F. Antón-Tay, Melatonin modifies calmodulin cell levels in MDCK and N1E-115 cell lines and inhibits phosphodiesterase activity in vitro, Brain Res. 557 (1–2) (1991) 289–292.
[90] N. Takuwa, W. Zhou, Y. Takuwa, Calcium, calmodulin and cell cycle progression, Cell. Signal. 7 (2) (1995) 93–104.
[91] J. Dai, E.W. Inscho, L. Yuan, S.M. Hill, Modulation of intracellular calcium and calmodulin by melatonin in MCF-7 human breast cancer cells, J. Pineal Res. 32 (2) (2002) 112–119.
[92] F. Sadoughi, P. Maleki Dana, Z. Asemi, B. Yousefi, Targeting microRNAs by curcumin: implication for cancer therapy, Crit. Rev. Food Sci. Nutr. (2021) 1–12.
[93] P. Liu, X. Xie, A. Yang, Y. Kong, D. Allen-Gipson, Z. Tian, et al., Melatonin regulates breast cancer progression by the lnc010561/miR-30/FKBP3 Axis, Mol. Ther. Nucleic Acids 19 (2020) 765–774.
[94] A. Yang, F. Peng, L. Zhu, X. Li, S. Ou, Z. Huang, et al., Melatonin inhibits triple-negative breast cancer progression through the Lnc049808-FUNDC1 pathway, Cell Death Dis. 12 (8) (2021) 712.
[95] L.C. Ferreira, F. Orso, D. Dettori, J.Z. Lacerda, T.F. Borin, D. Taverna, et al., The role of melatonin on miRNAs modulation in triple-negative breast cancer cells, PLoS One 15 (2) (2020), e0228062.
[96] J.H.M. Marques, A.L. Mota, J.G. Oliveira, J.Z. Lacerda, J.P. Stefani, L.C. Ferreira, et al., Melatonin restrains angiogenic factors in triple-negative breast cancer by targeting miR-152-3p: in vivo and in vitro studies, Life Sci. 208 (2018) 131–138.
[97] P. Lissoni, S. Barni, M. Mandalà, A. Ardizzoia, F. Paolorossi, M. Vaghi, et al., Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status, Eur. J. Cancer 35 (12) (1999) 1688–1692.
[98] P. Lissoni, S. Barni, S. Meregalli, V. Fossati, M. Cazzaniga, D. Esposti, et al., 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 (4) (1995) 854–856.
[99] E.S. Schernhammer, A. Giobbie-Hurder, K. Gantman, J. Savoie, R. Scheib, L.M. Parker, et al., A randomized controlled trial of oral melatonin supplementation and breast cancer biomarkers, Cancer Causes Control : CCC (Cancer Causes Control) 23 (4) (2012) 609–616.
[100] P. Lissoni, G. Tancini, F. Paolorossi, M. Mandalà, A. Ardizzoia, F. Malugani, et al., Chemoneuroendocrine therapy of metastatic breast cancer with persistent thrombocytopenia with weekly low-dose epirubicin plus melatonin: a phase II study, J. Pineal Res. 26 (3) (1999) 169–173.
[101] A.C.S. Palmer, M. Zortea, A. Souza, V. Santos, J.V. Biazús, I.L.S. Torres, et al., Clinical impact of melatonin on breast cancer patients undergoing chemotherapy; effects on cognition, sleep and depressive symptoms: a randomized, double-blind, placebo-controlled trial, PLoS One 15 (4) (2020), e0231379.
[102] P.F. Innominato, A.S. Lim, O. Palesh, M. Clemons, M. Trudeau, A. Eisen, et al., The effect of melatonin on sleep and quality of life in patients with advanced breast cancer, Support. Care Cancer : Off. J. Multinatl. Assoc. Support. Care Canc. 24 (3) (2016) 1097–1105.
[103] M.V. Hansen, L.T. Andersen, M.T. Madsen, I. Hageman, L.S. Rasmussen, S. Bokmand, et al., Effect of melatonin on depressive symptoms and anxiety in patients undergoing breast cancer surgery: a randomized, double-blind, placebo-controlled trial, Breast Cancer Res. Treat. 145 (3) (2014) 683–695.
[104] A. Sedighi Pashaki, K. Mohammadian, S. Afshar, M.H. Gholami, A. Moradi, S.A. Javadinia, et al., A randomized, controlled, parallel-group, trial on the effects of melatonin on fatigue associated with breast cancer and its adjuvant treatments, Integr. Cancer Ther. 20 (2021), 1534735420988343.
[105] world cancer research fund, Global cancer incidence: both sexes [Available from: https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data, 2019.