Review Article

Ahmad Fazilat, Salomeh Roshani, Fatemeh Mortazavi Moghadam and Mohammad Valilo*

An overview of the relationship between melatonin and drug resistance in cancers

https://doi.org/10.1515/hmbci-2025-0016
Received February 25, 2025; accepted April 26, 2025;
published online May 22, 2025

Abstract: The most common methods of treating cancer are surgery, chemotherapy, and radiotherapy. However, given that some cancers are not operable, the best method is chemotherapy and radiotherapy. Over time, people become resistant to chemotherapy drugs, and increasing the dose of the drug leads to damage to normal cells. In this article, various sources such as Google Scholar, PubMed, and Semantic Scholar were used, and articles between 1997 and 2025 that were relevant to our topic were selected. Various factors are involved in drug resistance. Melatonin is a hormone that has various roles in the body. One of its most important functions is regulating the circadian rhythm of sleep and its anti-inflammatory and antioxidant properties. According to studies, melatonin plays a role in the treatment of some diseases and cancers. The roles of melatonin in cancer treatment include anti-apoptotic, anti-angiogenic, and anti-migratory effects, as well as drug resistance and cell cycle regulation. As mentioned, one of the main reasons for the failure of cancer treatment is drug resistance, and the role of melatonin in drug resistance in cancers has been proven. Therefore, in this study, our goal is to investigate the mechanisms through which melatonin plays a role in drug resistance in different types of cancer.

Keywords: colorectal cancer; drug resistance; melatonin; hepatocellular carcinoma; chemotherapy

***Corresponding author: Mohammad Valilo**, Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran, E-mail: valilo.biomed@gmail.com
Ahmad Fazilat, Department of Genetics, Motamed Cancer Institute, Breast Cancer Research Center, ACECR, Tehran, Iran
Salomeh Roshani, Department of Biology, Faculty of Natural Science, University of Tabriz, Tabriz, Iran
Fatemeh Mortazavi Moghadam, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

Introduction

Common treatments for cancer include surgery, chemotherapy, radiation therapy, endocrine therapy, immunotherapy, and targeted therapy. Despite the progress achieved in cancer treatment, drug resistance is still a major challenge in treatment and a cause of mortality [1, 2]. Different factors including genetics, epigenetics, existence of cancer stem cells, pH, induction of hypoxia, autophagy, faulty miRNA regulation, and environmental factors, as well as cellular and molecular mechanisms, are involved in drug resistance [3–5]. Considering that most of the findings obtained about the resistance of tumors to chemotherapy are derived from tumor xenograft research and cell culture experiments in laboratory conditions, they do not accurately predict the conditions of tumor cells inside the human body [6]. In order to effectively treat tumors with chemotherapy drugs, the drugs must pass through the blood vessel wall and enter the tumor tissue and cancer cells. It has been reported that the distribution of drugs in tumor tissues is not uniform and not all cells are equally exposed to chemotherapy drugs [7]. In traditional treatments, most chemotherapy drugs directly affect DNA and cause the destruction of cancer cells by damaging DNA. Most of these drugs have significant therapeutic effects in the early stages of treatment, but with the passage of time, their efficacy decreases, and cancer cells become resistant to them. For example, about a fifth of children with acute lymphoblastic leukemia and almost half of individuals with small cell lung cancer experience relapse after treatment [8, 9].

Melatonin is a hormone derived from the amino acid tryptophan, which is produced in different parts of the body. The main source of melatonin production in the body is the pineal gland. Melatonin is generated in a circadian rhythm in the dark. It stimulates the target organs and enhances the body's resistance to various diseases by entering the homeostatic rhythm [10, 11]. Growing studies have indicated that melatonin plays a variety of roles in different pathways, including oxidative stress, immune modulation, and cell protection. Melatonin exhibits various anti-cancer activities. The effects of melatonin on different cellular mechanisms,

including apoptosis, cell proliferation, cell migration, metastasis, drug resistance, and colony formation, have been investigated, and it has been reported that melatonin can be effective in cancer treatment by interacting with these mechanisms [12–14]. The inactivation of drugs is a complex process in which different mechanisms are involved. Among these mechanisms, an increase in P-glycoprotein (P-gp) efflux pump, ATP-binding cassette (ABC), and anti-apoptotic molecules, as well as a decrease in pro-apoptotic molecules and epigenetic changes can be mentioned [15–17]. Studies have shown that melatonin sensitizes cancer cells to drugs through overcoming drug resistance mechanisms. Therefore, in this review, we aimed to investigate the mechanisms through which melatonin reduces drug resistance in various cancers.

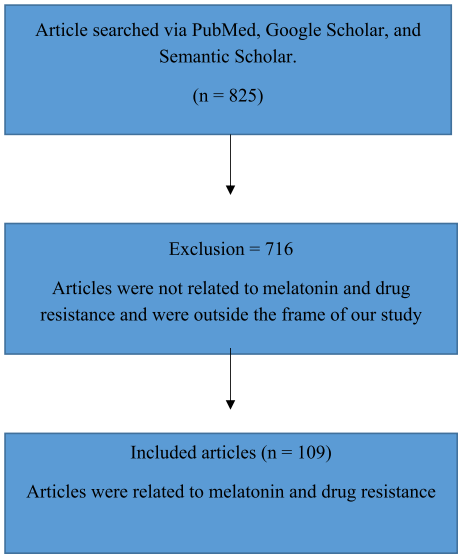

Figure 1: Flowchart of the article search.

Methods

This study included a search for relevant articles in Google Scholar, PubMed, and Semantic Scholar. Articles were searched for five months according to keywords “melatonin” and “drug resistance”. Studies that were related to our research topic were selected, and articles with their abstracts or full texts in English were reviewed. The selected articles were published between 1997 and 2025. The purpose of this review was to identify the latest articles and achievements related to the subject of our study. Articles outside the time frame of our study, those written in a language other than English, and those not related to the topic of our research were excluded from the study. The search framework of the articles is shown in Figure 1 (Figure 1).

Melatonin

Melatonin is a term derived from two Greek words: “molasses” meaning dark and “tonus” meaning darkness hormone. The first step in the production of melatonin in the pineal gland is the hydroxylation of the amino acid tryptophan. Next, 5-hydroxytryptophan is decarboxylated by a decarboxylase enzyme and produces 5-hydroxytryptamine (serotonin). Then serotonin is acetylated and methylated through two consecutive reactions to produce melatonin. While the main source of melatonin is the pineal gland, it is also produced in smaller quantities in other parts of the body such as the digestive system, lymphocytes, and the retina. In addition, melatonin is also found in different parts of higher plants, including seeds and leaves [18–22]. The roles of melatonin in plants include increasing resistance to oxidative stress, controlling shoot closure, aiding in germination, and acting as an anti-stress agent against ultraviolet radiation, heavy metals, drought, and salinity [23]. Melatonin usually exerts its effects in an autocrine, paracrine, and endocrine manner. Melatonin receptors exist in the cell membrane, inside the cell, or in the cell nucleus (orphan nuclear receptors). In humans, melatonin mainly exerts its effects through membrane-bound G protein-coupled receptors (GPCR), which include three types: MT1, MT2, and MT3. ML1 (high affinity) and ML2 (low affinity) are two types of melatonin receptors. ML1 includes MT1 and MT2 and acts through GPCRs, while ML2, which includes MT3, belongs to the quinone reductase family [22, 24–27]. The antioxidant role of melatonin is the opposite in normal and cancer cells. Melatonin produced from non-pineal gland cells acts on melatonin receptors after being released from mitochondria into the cytoplasm. Melatonin removes free radicals from mitochondria through two pathways: directly removing free radicals and reactive oxygen species (ROS) and indirectly increasing the activity and expression of antioxidant enzymes [28–30]. In tumor cells, melatonin increases the levels of ROS via two mechanisms: In the first mechanism, it stimulates electron transport chain (ETC) complexes (I and III), leading to the production of ROS and free radicals by these complexes, and in the second mechanism, melatonin disrupts the balance of oxidant and antioxidant compounds by reducing the number of antioxidant molecules [31–33]. Melatonin decreases tumor cell survival through the inhibition of the extracellular regulated protein kinase (ERK) and Akt pathway. The inhibition of the ROS-dependent Akt pathway increases Bax and decreases Bcl-2 and cyclin D1 in tumor cells. Moreover, melatonin promotes apoptosis by influencing the expression

of MDM2, which inhibits p53 and induces the activity of caspase-3 and -9 [34].

The activation of caspase-3 and -9 by melatonin also implies that by inhibiting the PI3K/Akt and p300/NF-B, COX-2/prostaglandin E 2 (PGE2) pathways, melatonin increases the expression of Apaf-1 and releases cytochrome *c* and finally activates caspase-3 and caspase-9 [35, 36]. Over the last decades, many studies have investigated the anti-cancer effects of melatonin and have confirmed its protective effects against cancer. Cytotoxic and cytostatic actions and the reduction of neoplastic enhancement are among the most prominent roles of melatonin in combating cancer [37]. Melatonin regulates cancer cells through various mechanisms including interaction with the Wnt/beta-catenin signaling pathway, regulation of histone modification, and increase of mitochondrial ROS. For example, in gastric cancer, melatonin inhibits cancer cell growth by interfering with autophagy, endoplasmic reticulum (ER) stress, and the Ras-Raf-ERK signaling pathway [38–40]. One anticancer role of melatonin is to reduce cell migration. Matrix metalloproteinase (MMP)-2 and MMP-9 are the most important MMPs involved in metastasis, which contribute to the degradation of the basement membrane and extracellular matrix (ECM) [41]. The expression of vimentin, α-SMA, and N-cadherin, which are indicators of the epithelial-mesenchymal transition (EMT) phenomenon, decreases under the influence of melatonin. In the phenomenon of EMT, cells lose their epithelial properties (polarization and adhesion) and acquire mesenchymal properties (invasion and migration), which indicates the anti-migratory and invasive properties of melatonin [42, 43] (Figure 2).

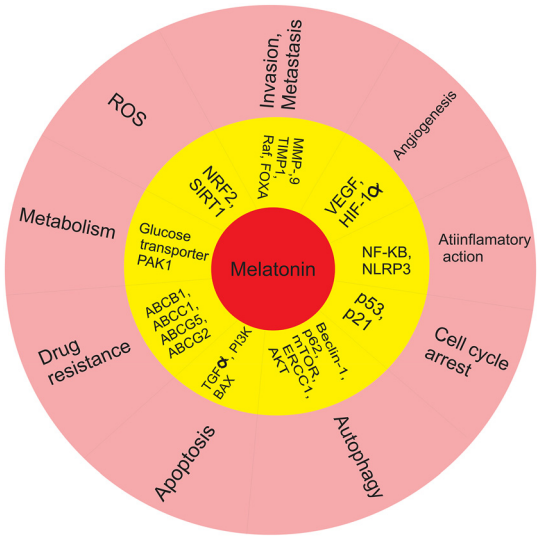

Figure 2: The summarized function of melatonin in different cancer hallmarks. ABC: ATP binding cassette; AKT: Protein kinase B; Bax: Bcl-2-associated protein x; ROS: Reactive oxygen species; NF-κB: Nuclear factor kappa B; nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; VEGF: Vascular endothelial growth factor; HIF-1α: Hypoxia-inducible factor 1-alpha; MMP: Matrix metalloproteinase; RAF-1: Rapidly accelerated fibrosarcoma-1; FOXA: Fox corporation class A common stock; NRF2: Nuclear factor erythroid 2–related factor; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol-3 kinase; SIRT1: Silent information regulator Sirtuin 1.

Drug resistance

Considering that cancer is an emerging disease, which is usually incurable, finding effective treatments is a primary objective for medical professionals and researchers. Despite the fact that one of the most promising methods to treat cancer is chemotherapy, more than 90 % of chemotherapy attempts fail due to the resistance of cancer cells to chemotherapy drugs. Various factors including microRNAs, genetics, long non-coding RNAs (lncRNAs), and ABC transporters are involved in the development of multidrug resistance (MDR) in cancer cells [44–48]. Recent findings have shown that the probability of drug resistance in single-drug treatments is higher than in multi-drug treatments; therefore, the probability of drug resistance decreases in multi-drug treatments [49]. Understanding the mechanisms that cause resistance is crucial. Some factors such as autophagy and hypoxia play a role in drug resistance. According to the World Health Organization, cancer is the second leading cause of death in the world. Therefore, while cancers that respond to chemotherapy drugs can be treated, for the treatment of cancers that are resistant to drugs, identifying the mechanisms and drugs that lead to the reduction of drug resistance is a critical goal [50–52]. Cancer cells respond well to chemotherapy drugs in the early stages of treatment, but gradually they develop resistance to drugs. Drug resistance can be acquired (caused by environmental factors) or intrinsic (caused by internal factors). According to reports, there are two types of MDR in tumor cells: in the first type, MDR is inherent to cytotoxic agents, while the second type acquires the chemotherapy resistance phenotype during drug therapy [53, 54]. From another point of view, MDR can be divided into two types: cellular and non-cellular. The cellular mechanism is further divided into classical and non-classical types. The classical mechanism involves membrane transporter systems that lead to a decrease in the intracellular concentration of the drug, with these proteins belonging to the ATP-binding cassette (ABC) family. The non-classical mechanism involves enzymes that reduce enzyme activity without changing the enzyme concentration [55, 56].

Modification of histones (phosphorylation and acetylation) regulates the expression of ABCG2. Decreased H3K9

trimethylation allows promoter accessibility for chromatin-remodeling RNA polymerase II and Brahma protein-related gene 1 (Brg1), leading to the transcriptional activation of ABCG2 [57]. The most important ABC group is P-gp, which is a membrane protein that acts through an ATP-dependent pump. P-gp substrates include xenobiotics, antiviral protease inhibitors, anthracyclines, alkaloids, and other antibiotics, which reduce the bioavailability of therapeutic drugs, while protecting healthy cells from toxic substances [58–60]. According to the findings, high expression of membrane P-gp in cells with MDR is not always associated with high activity of these proteins, because the phenomena of phosphorylation and acetylation may affect the relationship between MDR and P-gp [61–63]. Replacement of P-gp phosphoryl residues by protein kinase A (PKA) and protein kinase C (PKC) affects P-gp activity [64]. Through the inhibition of PKC-α in soft tissue cells, p53 negatively regulates P-gp phosphorylation and sensitivity of cells to chemotherapy drugs [63]. Studies have shown that there are two substrate binding sites in P-gp, which determine the type of substrate that binds to P-gp and have modular activities. However, one substrate can regulate the transport of the other substrate by affecting both binding sites [65, 66]. Two different types of substrates may bind to the same site at the same time, and different binding sites may bind to the same substrates or be allosterically dependent [67]. It has been reported that P-gp structural changes have significant effects on ATPase activity and drug transport [68]. Research on ABCB1 gene polymorphisms has shown that these polymorphisms may affect tissue expression, drug elimination status, disease risk, and treatment by altering P-gp transporter function [69]. For example, in childhood acute lymphoblastic leukemia, the presence of 3,435 TT and CT genotypes compared to the CC genotype leads to increased permeability of the substrates in P-gp [70]. Research on colon cancer cells has revealed that the expression and secretion of endothelin-1 are inhibited by melatonin in these cells. The inhibition of endothelin-1 suppresses the transcription factors nuclear factor kappa B (NF-kβ) and FoxO1-1 and has a negative effect on the growth and progression of cancer [71].

Tumor microenvironment (TME) in cancer drug resistance

The TME is an ever-changing and complex milieu that is believed to be rogue. The TME consists of the ECM, stroma, blood supply, immune cells, and the lymphatic system. Using benign and malignant cells, a harsh environment, and an immunosuppressive system, these complex components create phenotypic diversity and flexibility in cancer cell growth and proliferation [72, 73]. One characteristic of the TME responsible for ECM remodeling, immune evasion, and therapeutic resistance is cell-to-ECM communication and cell-cell interactions [72, 74]. Factors that contribute to treatment resistance within the TME include microRNAs, abnormal mechanical forces, metabolic disorders, a hypoxic environment, and exosomes generated by benign and malignant cells [74, 75]. Stem cells are located in a microenvironment called the stem cell niche, and various soluble factors in the cell niche protect the stem cells. Stem cells are selected for self-renewal and aging through molecular signals and interactions with other cells. Cancer stem cells in the TME use immune and stromal cells for their growth, and this intersection of tumor and stromal cells leads to angiogenesis and effective immune escape in the TME [76–78].

The TME niche becomes acidified due to hypoxia and high lactate, changing the conditions for oncogenesis. The intracellular pH in cancer cells is higher compared to healthy cells, and this causes the inhibition of apoptosis and the increase of cell proliferation in cancer cells, while the extracellular pH is lower. Niche acidity in the direction of increasing lactate suppresses the cytotoxicity of infiltrating T cells and induces tumor-associated macrophages (TAMs) M2 polarization. According to the literature, niche acidity leads to EMT and invasion in breast cancer, neuroblastoma, and melanoma [79–81]. Due to the ion trapping phenomenon, the difference in pH between the inside and outside of the cells in the cell niche prevents proper distribution and absorption of the drug, and in the extracellular acid environment, the ionization of the open agents is hindered by their passage through this barrier [82, 83]. Conversely, weak acids have high intracellular permeability. For example, paclitaxel, which is a non-ionized agent, is not blocked by this barrier. This theory of ion trapping can help therapeutic methods in the future [84, 85]. On the other hand, low pH caused by hypoxia and low perfusion through epigenetic changes, especially in p53, inhibit apoptosis and induce P-gp activity to stimulate MDR. The acidic niche induces cellular dormancy by inhibiting the cell cycle in the G2/M phase in studies of radioresistance and/or chemotherapy [86].

The instability of the genome caused by the acidic environment via phenotypic changes is another factor contributing to resistance to treatment [87].

Melatonin in cancer drug resistance

It has been reported that melatonin inhibits adenylyl cyclase and decreases the expression of cAMP, PKA, PKC, and mitogen-activated protein kinases (MAPKs) through the

membrane receptor MT1, which has a negative effect on the expression of genes involved in migration, angiogenesis, proliferation, and phosphorylation of CREB transcription factor [65, 66, 88]. Growing studies indicate that the physical state of the lipid bilayer in P-gp plays a role in both the binding and hydrolysis of ATP. Melatonin affects membrane dynamics in different ways at different concentrations. High concentrations of melatonin reduce membrane cellulite, and on the contrary, low concentrations increase membrane cellulite. At higher concentrations of melatonin, there is a uniform distribution of melatonin in the membrane, while at low concentrations, there are small domains enriched with melatonin with a thin thickness in the membrane [68]. The data obtained from X-ray diffraction showed that melatonin molecules are positioned in a crystalline form within the membrane, and one melatonin molecule is connected to two fat molecules. Understanding the organization of melatonin in biological membranes can shed light on the relationship between the effect of melatonin and P-gp activity [68].

Hepatocellular carcinoma (HCC) is a type of malignant tumor that occurs in both sexes. Since this disease does not manifest itself in its early stages, most patients suffering from this disease miss primary treatments and must undergo chemotherapy. Due to the complex molecular and cellular mechanisms that occur in these cells, they usually become resistant to treatment, and increasing the dose of the drug leads to side effects and diminished quality of life. Therefore, finding a therapeutic drug with fewer side effects is essential [89]. As mentioned in the previous sections, in addition to its role in nighttime sleep, melatonin has other properties such as antioxidant, anti-inflammatory, anti-invasion, and anti-cancer activities. One of the significant functions of melatonin is that it adversely affects drug resistance in cancer. One of the chemotherapy drugs used in liver cancer cells is doxorubicin (DOX). The study by Hamed et al. on HepG2 cells showed that by increasing the dose of DOX, the levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, MCP-1, interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and the expression of ABC family members increase. Subsequent treatment with melatonin decreased migration, differentiation, and the expression of ABC transporters including ABCB1, ABCC1, ABCC5, and ABCG2 [89–92].

Martín et al. reported that melatonin inhibited ABCB1 expression in large B-cell lymphoma cells treated with epirubicin [93]. The research by Hsieh et al. showed that melatonin inhibits the ABCB1 gene in vincristine-resistant oral cancer cell lines through the increase of microRNA-34b [94]. Another study showed that in individuals with chronic pancreatitis, melatonin treatment reduces the expression of ABCC5 and ABCG2 genes [95]. As mentioned, various mechanisms regulate the expression of ABC transporters. One of these mechanisms is the epigenetic process. The study by To et al. revealed that the methylation of the active CpG island in the promoter region of ABCG2/BCRP leads to the inhibition of this transporter [96]. Martín et al. found that in individuals with glioblastoma tumors, the ABCG2 promoter methylation is lower than in normal individuals, which indicates the higher expression of ABCG2 in patients with glioblastoma. When glioblastoma tumor cells were treated with melatonin, the methylation level of the ABCG2 promoter increased, which led to a decrease in ABCG2 transporter expression and an increase in the toxic effects of chemotherapy drugs and melatonin [97].

Martín et al. also reported that melatonin upregulates DNA methyltransferase activity, and 5-azacitidine (AZA) can inhibit the effects of melatonin on ABCG2/BCRP expression [97]. The study by Magdalena et al. revealed that in colon cancer cells, treatment with melatonin alone had no effect on P-gp expression, but the simultaneous use of melatonin and DOX led to increased P-gp expression and ABCB1 levels [53]. In colorectal cancer, Oct4 and cellular prion protein (PrP) are related to tumor grade and metastasis. In patients with colorectal cancer, combined treatment of melatonin and 5-fluorouracil (5-FU) causes the negative regulation of stem cell markers including Sox2, ALDH1A1, Oct4, and Nanog by suppressing PrPC. As a result, cancer growth, differentiation, migration, and angiogenesis are inhibited [98]. Another study demonstrated that when melatonin is used in combination with oxaliplatin, it leads to the apoptosis of oxaliplatin-resistant colorectal cancer cells by inhibiting PrPC [99].

Increased expression of PrPC, through the mediators of catalase and superoxide dismutase (SOD) enzymes, plays an essential role in creating oxaliplatin drug resistance in colorectal cancer cells, and superoxide anion usually decreases in oxaliplatin-resistant cancer cells. In addition, by inhibiting PrPC in oxaliplatin-resistant cancer cells, melatonin increases apoptosis and ER stress and significantly inhibits oxaliplatin-related catalase and SOD [99]. According to the findings, hypoxia leads to the resistance of cancer cells to chemotherapy drugs and radiotherapy. Hypoxia alters TME physiological conditions by upregulating hypoxia-inducible factor-1 (HIF-1) and targeting a number of regulatory genes in favor of MDR and promoting angiogenesis [100, 101]. Studies on gastric cancer cells have shown that melatonin induces procaspase enzymes and sensitizes cancer cells to cisplatin by suppressing NF-κB and stimulating p38 and JNK [102]. According to the experiments, combining a ketogenic diet (low glucose) with melatonin

reduces the function of drug-resistance pumps and leads to the reduction of drug resistance in breast cancer cells through the reduction of ATP production. Additionally, melatonin acts as an angiogenesis inhibitor and apoptosis inducer [103].

In the study by Martin et al., it was observed that melatonin inhibits BCRP expression by inducing BCRP promoter methylation. However, dim light exposure at night (dLEN) leads to the suppression of intratumoral DOX levels through the disruption of melatonin production [97]. Another study in this field showed that melatonin inhibits the phospho-activation of STAT3 by inhibiting the upstream signaling pathways of STAT3 and leads to the inhibition of chemotherapy resistance in breast cancer cells [104]. According to the findings, melatonin also reduces drug resistance in cancer cells by using miRNAs as intermediates. One study demonstrated that melatonin increased the expression of miR-34b-5p and miR-892a, induced ABCB1 and ABCB4, and increased the sensitivity of MDR-resistant oral cancer cell lines to vincristine [94]. It has been reported that one of the pathways through which melatonin interferes with drug resistance in cancer cells involves the tensin homolog deleted on chromosome ten (PTEN). In the study by Xu et al., it was reported that in gastric cancer cells, the inhibition of the PTEN pathway leads to resistance to DOX. In this regard, melatonin increases the sensitivity of cancer cells to chemotherapy drugs and reduces drug resistance by inhibiting the PI3K/PTEN pathway [105, 106]. Additionally, another study showed that melatonin enhances the toxic effects of DOX in leukemia cancer cells by upregulating PTEN and downregulating P-gp [107]. Melatonin also regulates the phosphorylation and transactivation of ERα, and the reduction of melatonin by increasing the phosphorylation of ERα at S118 and S167 contributes to tamoxifen drug resistance [108]. Sakatani et al. revealed that in 5-FU-resistant cells, melatonin reduces thymidylate synthase transcript and protein expression, and the suppression of thymidylate synthase leads to cell death [109]. According to these studies, melatonin can affect drug resistance factors and mechanisms in different cancers through different pathways. As a result, melatonin can be used as an adjuvant treatment in various cancers.

Conclusion

Drug resistance is one of the main problems in the treatment of numerous diseases including cancer. It leads to treatment failure and ultimately an increase in burden to individuals and society, and an increase in drug dosage, which leads to damage to non-cancerous and peripheral tissues. Cancer cells develop drug resistance through various mechanisms, such as increasing the number and efficiency of ABC transporters, inactivating drugs, changing drug targets, and reducing drug absorption. Melatonin is a hormone used in different cancer treatments. According to studies, one of the roles of melatonin in the treatment of cancer is intervening in drug resistance. By targeting these drug resistance mechanisms, melatonin leads to the reduction of drug resistance in cancer cells, and therefore, can be used as a therapeutic target in cancer treatment, which requires more studies in this field.

Acknowledgments: We thank the Urmia University of Medical Sciences for all support of this research.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: F.M, and A.F. were involved in writing the article. S.R. was involved in drawing figures. M. V. participated in the study design.
Use of Large Language Models, AI and Machine Learning Tools: NO.
Conflict of interest: NO.
Research funding: NO.
Data availability: NO.

References

1. Rueff J, Rodrigues AS. Cancer drug resistance: a brief overview from a genetic viewpoint. Cancer Drug Resist: Overv Methods 2016:1–18. https://doi.org/10.1007/978-1-4939-3347-1_1.
2. Sargazi Z, Yazdani Y, Tahavvori A, Youshanlouei HR, Alivirdiloo V, Beilankouhi EAV, et al. NFR2/ABC transporter axis in drug resistance of breast cancer cells. Mol Biol Rep 2023;50:5407–14.
3. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist 2019;2:141.
4. Si W, Shen J, Zheng H, Fan W. The role and mechanisms of action of microRNAs in cancer drug resistance. Clin Epigenet 2019;11:1–24.
5. Amiri R, Nabi PN, Fazilat A, Roshan F, Nouhi Kararoudi AN, Hemmati-Dinarvand M, et al. Crosstalk between miRNAs and signaling pathways in the development of drug resistance in breast cancer. Horm Mol Biol Clin Investig 2025;46:47–55.
6. Ma Y, Lin Z, Fallon JK, Zhao Q, Liu D, Wang Y, et al. New mouse xenograft model modulated by tumor-associated fibroblasts for human multi-drug resistance in cancer. Oncol Rep 2015;34:2699–705.
7. Dewhirst MW, Secomb TW. Transport of drugs from blood vessels to tumour tissue. Nat Rev Cancer 2017;17:738–50.
8. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242.
9. O'Connor D, Sibson K, Caswell M, Connor P, Cummins M, Mitchell C, et al. Early UK experience in the use of clofarabine in the treatment of relapsed and refractory paediatric acute lymphoblastic leukaemia. Br J Haematol 2011;154:482–5.

10. Talib WH. Melatonin and cancer hallmarks. Molecules 2018;23. https://doi.org/10.3390/molecules23030518.
11. Li Y, Li S, Zhou Y, Meng X, Zhang JJ, Xu DP, et al. Melatonin for the prevention and treatment of cancer. Oncotarget 2017;8:39896–921.
12. Hulvat MC. Cancer incidence and trends. Surg Clin North Am 2020;100: 469–81.
13. Arbiser JL, Bonner MY, Gilbert LC. Targeting the duality of cancer. NPJ Precis Oncol 2017;1. https://doi.org/10.1038/s41698-017-0026-x.
14. Chen L, Liu L, Li Y, Gao J. Melatonin increases human cervical cancer HeLa cells apoptosis induced by cisplatin via inhibition of JNK/Parkin/ mitophagy axis. In Vitro Cell Dev Biol Anim 2018;54:1–10.
15. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. Cancers (Basel) 2014;6: 1769–92.
16. Xiao Y, Hassani M, Barahouei Moghaddam M, Fazilat A, Ojarudi M, Valilo M. Contribution of tumor microenvironment (TME) to tumor apoptosis, angiogenesis, metastasis, and drug resistance. Med Onco 2025;42:1–14.
17. Lahtz C, Pfeifer GP. Epigenetic changes of DNA repair genes in cancer. J Mol Cell Biol 2011;3:51–8.
18. Ahmad SB, Ali A, Bilal M, Rashid SM, Wani AB, Bhat RR, et al. Melatonin and health: insights of melatonin action, biological functions, and associated disorders. Cell Mol Neurobiol 2023;43:2437–58.
19. Coon SL, Weller JL, Korf HW, Namboodiri M, Rollag M, Klein DC. cAMP regulation of Arylalkylamine N-acetyltransferase (AANAT, EC 2.3. 1.87): a NEW cell line (1E7) provides evidence of intracellular aanat activation. J Biol Chem 2001;276:24097–107.
20. Reiter RJ, Tan DX, Galano A. Melatonin: exceeding expectations. Physiology 2014;29:325–33.
21. Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. Dig Dis Sci 2002;47:2336–48.
22. Jalilzadeh KAS, Kalashipour CG, Heydari P, Fazilat A, Mortazavi Moghadam F, Valilo M. Hormonal disorders in autism spectrum disorders. Horm Mol Biol Clin Invest 2025. https://doi.org/10. 1515/hmbci-2024-0078.
23. Tan DX, Hardeland R, Manchester LC, Korkmaz A, Ma S, Rosales-Corral S, et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. J Exp Bot 2012;63: 577–97.
24. Li DY, Smith DG, Hardeland R, Yang MY, Xu HL, Zhang L, et al. Melatonin receptor genes in vertebrates. Int J Mol Sci 2013;14:11208–23.
25. Jockers R, Delagrange P, Dubocovich ML, Markus RP, Renault N, Tosini G, et al. Update on melatonin receptors: IUPHAR Review 20. Br J Pharmacol 2016;173:2702–25.
26. Hardeland R. Melatonin in aging and disease–multiple consequences of reduced secretion, options and limits of treatment. Aging Dis 2012; 3:194.
27. Uz T, Arslan AD, Kurtuncu M, Imbesi M, Akhisaroglu M, Dwivedi Y, et al. The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. Mol Brain Res 2005;136:45–53.
28. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, et al. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019. JAMA Oncol 2022;8:420–44.
29. Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J. Cancer: a systems biology disease. Biosystems 2006;83:81–90.
30. Suofu Y, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J, et al. Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. Proc Natl Acad Sci 2017;114:E7997–8006.
31. Bizzarri M, Proietti S, Cucina A, Reiter RJ. Molecular mechanisms of the pro-apoptotic actions of melatonin in cancer: a review. Expert Opin Ther Targets 2013;17:1483–96.
32. Martín M, Macías M, León J, Escames G, Khaldy H, Do AC. Melatonin increases the activity of the oxidative phosphorylation enzymes and the production of ATP in rat brain and liver mitochondria. Int J Biochem Cell Biol 2002;34:348–57.
33. Ammar OA, El-Missiry MA, Othman AI, Amer ME. Melatonin is a potential oncostatic agent to inhibit HepG2 cell proliferation through multiple pathways. Heliyon 2022;8. https://doi.org/10.1016/j.heliyon. 2022.e08837.
34. Liu R, Wang HL, Deng MJ, Wen XJ, Mo YY, Chen FM, et al. Melatonin inhibits reactive oxygen species-driven proliferation, epithelial-mesenchymal transition, and vasculogenic mimicry in oral cancer. Oxid Med Cell Longev 2018;2018. https://doi.org/10.1155/2018/ 3510970.
35. Proietti S, Cucina A, Dobrowolny G, D'Anselmi F, Dinicola S, Masiello MG, et al. Melatonin down-regulates MDM 2 gene expression and enhances p53 acetylation in MCF-7 cells. J Pineal Res 2014;57: 120–9.
36. Song J, Ma SJ, Luo JH, Liu H, Li L, Zhang ZG, et al. Downregulation of AKT and MDM2, melatonin induces apoptosis in AGS and MGC803 Cells. Anat Rec 2019;302:1544–51.
37. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M, Dubocovich ML. MT1 and MT2 melatonin receptors: a therapeutic perspective. Annu Rev Pharmacol Toxicol 2016;56:361–83.
38. Florido J, Martinez-Ruiz L, Rodriguez-Santana C, López-Rodríguez A, Hidalgo-Gutiérrez A, Cottet-Rousselle C, et al. Melatonin drives apoptosis in head and neck cancer by increasing mitochondrial ROS generated via reverse electron transport. J Pineal Res 2022;73:e12824.
39. Zhang J, Xie T, Zhong X, Jiang HL, Li R, Wang BY, et al. Melatonin reverses nasopharyngeal carcinoma cisplatin chemoresistance by inhibiting the Wnt/β-catenin signaling pathway. Aging (Albany NY) 2020;12:5423.
40. Ma Z, Liu D, Di S, Zhang Z, Li W, Zhang J, et al. Histone deacetylase 9 downregulation decreases tumor growth and promotes apoptosis in non-small cell lung cancer after melatonin treatment. J Pineal Res 2019;67:e12587.
41. Brinckerhoff CE, Matrisian LM. Matrix metalloproteinases: a tail of a frog that became a prince. Nat Rev Mol Cell Biol 2002;3:207–14.
42. Custódio PR, Colombo J, Ventura FV, Castro TB, Zuccari DA. Melatonin treatment combined with TGF-β silencing inhibits epithelial-mesenchymal transition in CF41 canine mammary cancer cell line. Anti Cancer Agents Med Chem 2020;20:989–97.
43. Ridge KM, Eriksson JE, Pekny M, Goldman RD. Roles of vimentin in health and disease. Genes Dev 2022;36:391–407.
44. Chen X, Lu P, Wang DD, Yang SJ, Wu Y, Shen HY, et al. The role of miRNAs in drug resistance and prognosis of breast cancer formalin-fixed paraffin-embedded tissues. Gene 2016;595:221–6.
45. Han J, Sun W, Liu R, Zhou Z, Zhang H, Chen X, et al. Plasma exosomal miRNA expression profile as oxaliplatin-based chemoresistant biomarkers in colorectal adenocarcinoma. Front Oncol 2020;10:1495.
46. Jin KT, Lu ZB, Lv JQ, Zhang JG. The role of long non-coding RNAs in mediating chemoresistance by modulating autophagy in cancer. RNA Biol 2020;17:1727–40.
47. Ladd AD, Duarte S, Sahin I, Zarrinpar A. Mechanisms of drug resistance in HCC. Hepatology 2024;79:926–40.
48. To KK, Huang Z, Zhang H, Ashby JCR, Fu L. Utilizing non-coding RNA-mediated regulation of ATP binding cassette (ABC) transporters to

overcome multidrug resistance to cancer chemotherapy. Drug Resist Updates 2024;73:101058.
49. Cheng L, Li S, He K, Kang Y, Li T, Li C, et al. Melatonin regulates cancer migration and stemness and enhances the anti-tumour effect of cisplatin. J Cell Mol Med 2023;27:2215–27.
50. Datta S, Choudhury D, Das A, Mukherjee DD, Dasgupta M, Bandopadhyay S, et al. Autophagy inhibition with chloroquine reverts paclitaxel resistance and attenuates metastatic potential in human nonsmall lung adenocarcinoma A549 cells via ROS mediated modulation of β-catenin pathway. Apoptosis 2019;24:414–33.
51. Fu XT, Song K, Zhou J, Shi YH, Liu WR, Shi GM, et al. Tumor-associated macrophages modulate resistance to oxaliplatin via inducing autophagy in hepatocellular carcinoma. Cancer Cell Int 2019;19:1–11.
52. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: a brief review. Adv Pharmaceut Bull 2017;7:339.
53. Fic M, Gomulkiewicz A, Grzegrzolka J, Podhorska-Okolow M, Zabel M, Dziegiel P, et al. The impact of melatonin on colon cancer cells' resistance to doxorubicin in an in vitro study. Int J Mol Sci 2017;18: 1396.
54. Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging therapeutic strategies to overcome drug resistance in cancer cells. Cancers (Basel) 2024;16:2478.
55. Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med 2002;53:615–27.
56. Tan B, Piwnica-Worms D, Ratner L. Multidrug resistance transporters and modulation. Curr Opin Oncol 2000;12:450–8.
57. To KK, Polgar O, Huff LM, Morisaki K, Bates SE. Histone modifications at the ABCG2 promoter following treatment with histone deacetylase inhibitor mirror those in multidrug-resistant cells. Mol Cancer Res 2008;6:151–64.
58. Dewanjee S, Dua KT, Bhattacharjee N, Das A, Gangopadhyay M, Khanra R, et al. Natural products as alternative choices for P-glycoprotein (P-gp) inhibition. Molecules 2017;22:871.
59. Zhou S-F. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica 2008;38:802–32.
60. Zhang H, Xu H, Ashby JCR, Assaraf YG, Chen ZS, Liu HM. Chemical molecular-based approach to overcome multidrug resistance in cancer by targeting P-glycoprotein (P-gp). Med Res Rev 2021;41: 525–55.
61. Ullah MF. Cancer multidrug resistance (MDR): a major impediment to effective chemotherapy. Asian Pac J Cancer Prev APJCP 2008;9:1–6.
62. Ling V. Multidrug resistance: molecular mechanisms and clinical relevance. Cancer Chemother Pharmacol 1997;40:S3–8.
63. Szabó K, Bakos E, Welker E, Muller M, Goodfellow HR, Higgins CF, et al. Phosphorylation site mutations in the human multidrug transporter modulate its drug-stimulated ATPase activity. J Biol Chem 1997;272: 23165–71.
64. Bentley J, Quinn D, Pitman R, Warr J, Kellett G. The human KB multidrug-resistant cell line KB-C1 is hypersensitive to inhibitors of glycosylation. Cancer Lett 1997;115:221–7.
65. Ferreira RJ, Ferreira MJU, Dos Santos DJ. Do drugs have access to the P-glycoprotein drug-binding pocket through gates? J Chem Theor Comput 2015;11:4525–9.
66. Loo TW, Clarke DM. Attachment of a 'molecular spring'restores drug-stimulated ATPase activity to P-glycoprotein lacking both Q loop glutamines. Biochem Biophys Res Commun 2017;483:366–70.
67. Loo TW, Clarke DM. Do drug substrates enter the common drug-binding pocket of P-glycoprotein through "gates". Biochem Biophys Res Commun 2005;329:419–22.
68. Dies H, Cheung B, Tang J, Rheinstädter MC. The organization of melatonin in lipid membranes. Biochim Biophys Acta Biomembr 2015; 1848:1032–40.
69. Wolking S, Schaeffeler E, Lerche H, Schwab M, Nies AT. Impact of genetic polymorphisms of ABCB1 (MDR1, P-glycoprotein) on drug disposition and potential clinical implications: update of the literature. Clin Pharmacokinet 2015;54:709–35.
70. Fromm MF. The influence of MDR1 polymorphisms on P-glycoprotein expression and function in humans. Adv Drug Deliv Rev 2002;54: 1295–310.
71. León J, Casado J, Jiménez Ruiz SM, Zurita MS, González-Puga C, Rejón JD, et al. Melatonin reduces endothelin-1 expression and secretion in colon cancer cells through the inactivation of FoxO1 and NF-κβ J Pineal Res. 2014;56:415-26.
72. Khalaf K, Hana D, Chou JTT, Kaczmarek M, Mackiewicz A. Aspects of the tumor microenvironment involved in immune resistance and drug resistance. Front Immunol 2021;12:656364.
73. Kundu M, Butti R, Panda VK, Malhotra D, Das S, Mitra T, et al. Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. Mol Cancer 2024;23:92.
74. Sun Y. Tumor microenvironment and cancer therapy resistance. Cancer Lett 2016;380:205–15.
75. da Costa VR, Araldi RP, Vigerelli H, D'Ámelio F, Mendes TB, Gonzaga V, et al. Exosomes in the tumor microenvironment: from biology to clinical applications. Cells 2021;10:2617.
76. Hernández R, Jiménez-Luna C, Perales-Adán J, Perazzoli G, Melguizo C, Prados J. Differentiation of human mesenchymal stem cells towards neuronal lineage: clinical trials in nervous system disorders. Biomol Ther (Seoul) 2020;28:34.
77. Kidd S, Spaeth E, Watson K, Burks J, Lu H, Klopp A, et al. Origins of the tumor microenvironment: quantitative assessment of adipose-derived and bone marrow–derived stroma. PLoS One 2012;7:e30563.
78. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 2012;21:309–22.
79. Chiche J, Brahimi-Horn MC, Pouysségur J. Tumour hypoxia induces a metabolic shift causing acidosis: a common feature in cancer. J Cell Mol Med 2010;14:771–94.
80. Gillies RJ, Pilot C, Marunaka Y, Fais S. Targeting acidity in cancer and diabetes. Biochim Biophys Acta Rev Cancer 2019;1871:273–80.
81. Peppicelli S, Toti A, Giannoni E, Bianchini F, Margheri F, Del Rosso M, et al. Metformin is also effective on lactic acidosis-exposed melanoma cells switched to oxidative phosphorylation. Cell Cycle 2016;15: 1908–18.
82. LaMonte G, Tang X, Chen JLY, Wu J, Ding C-KC, Keenan MM, et al. Acidosis induces reprogramming of cellular metabolism to mitigate oxidative stress. Cancer Metabol 2013;1:1–19.
83. Gerweck LE, Vijayappa S, Kozin S. Tumor pH controls the in vivo efficacy of weak acid and base chemotherapeutics. Mol Cancer Ther 2006;5:1275–9.
84. Saunders DE, Lawrence WD, Christensen C, Wappler NL, Ruan H, Deppe G. Paclitaxel-induced apoptosis in MCF-7 breast-cancer cells. Int J Cancer 1997;70:214–20.
85. Lotz C, Kelleher DK, Gassner B, Gekle M, Vaupel P, Thews O. Role of the tumor microenvironment in the activity and expression of the p-glycoprotein in human colon carcinoma cells. Oncol Rep 2007;17: 239–44.
86. Ingangi V, Minopoli M, Ragone C, Motti ML, Carriero MV. Role of microenvironment on the fate of disseminating cancer stem cells. Front Oncol 2019;9:82.

87. Vander Linden C, Corbet C. Therapeutic targeting of cancer stem cells: integrating and exploiting the acidic niche. Front Oncol 2019;9:159.
88. Pourbarkhordar V, Rahmani S, Roohbakhsh A, Hayes AW, Karimi G. Melatonin effect on breast and ovarian cancers by targeting the PI3K/Akt/mTOR pathway. IUBMB Life 2024;76:1035–49.
89. Hamed AR, Yahya SM, Nabih HK. Anti-drug resistance, anti-inflammation, and anti-proliferation activities mediated by melatonin in doxorubicin-resistant hepatocellular carcinoma: in vitro investigations. N Schmied Arch Pharmacol 2023;396:1117–28.
90. Wang DY, Zou LP, Liu XJ, Zhu HG, Zhu R. Chemokine expression profiles of human hepatoma cell lines mediated by hepatitis B virus X protein. Pathol Oncol Res 2016;22:393–9.
91. Hou C, Lu L, Liu Z, Lian Y, Xiao J. Resveratrol reduces drug resistance of SCLC cells by suppressing the inflammatory microenvironment and the STAT3/VEGF pathway. FEBS Open bio 2021;11:2256–65.
92. Vyas D, Laput G, Vyas AK. Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis. OncoTargets Ther 2014: 1015–23. https://doi.org/10.2147/ott.s60114.
93. Liu K, Song J, Yan Y, Zou K, Che Y, Wang B, et al. Melatonin increases the chemosensitivity of diffuse large B-cell lymphoma cells to epirubicin by inhibiting P-glycoprotein expression via the NF-κB pathway. Transl Oncol 2021;14:100876.
94. Hsieh MJ, Lin CW, Su SC, Reiter RJ, Chen AWG, Chen MK, et al. Effects of miR-34b/miR-892a upregulation and inhibition of ABCB1/ABCB4 on melatonin-induced apoptosis in VCR-resistant oral cancer cells. Mol Ther Nucleic Acids 2020;19:877–89.
95. Tanoglu EG, Tanoğlu A, Meriçöz MÇA, Esen MF. Melatonin has favorable preventive effects on experimental chronic pancreatitis rat model. Turk J Med Sci 2021;51:2734–40.
96. To KK, Zhan Z, Bates SE. Aberrant promoter methylation of the ABCG2 gene in renal carcinoma. Mol Cell Biol 2006;26:8572–85.
97. Martín V, Sanchez-Sanchez AM, Herrera F, Gomez-Manzano C, Fueyo J, Alvarez-Vega MA, et al. Melatonin-induced methylation of the ABCG2/BCRP promoter as a novel mechanism to overcome multidrug resistance in brain tumour stem cells. Br J Cancer 2013;108:2005–12.
98. Lee JH, Yun CW, Han YS, Kim S, Jeong D, Kwon HY, et al. Melatonin and 5-fluorouracil co-suppress colon cancer stem cells by regulating cellular prion protein-Oct4 axis. J Pineal Res 2018;65:e12519.
99. Lee JH, Yoon YM, Han YS, Yun CW, Lee SH. Melatonin promotes apoptosis of oxaliplatin-resistant colorectal cancer cells through inhibition of cellular prion protein. Anticancer Res 2018;38:1993–2000.
100. Lv Y, Zhao S, Han J, Zheng L, Yang Z, Zhao L. Hypoxia-inducible factor-1α induces multidrug resistance protein in colon cancer. OncoTargets Ther 2015:1941–8. https://doi.org/10.2147/ott.s82835.
101. Warfel N, El-Deiry W. HIF-1 signaling in drug resistance to chemotherapy. Curr Med Chem 2014;21:3021–8.
102. Li W, Fan M, Chen Y, Zhao Q, Song C, Yan Y, et al. Melatonin induces cell apoptosis in AGS cells through the activation of JNK and P38 MAPK and the suppression of nuclear factor-kappa B: a novel therapeutic implication for gastric cancer. Cell Physiol Biochem 2015; 37:2323–38.
103. Talib WH. A ketogenic diet combined with melatonin overcomes cisplatin and vincristine drug resistance in breast carcinoma syngraft. Nutrition 2020;72:110659.
104. Xiang S, Dauchy RT, Hauch A, Mao L, Yuan L, Wren MA, et al. Doxorubicin resistance in breast cancer is driven by light at night-induced disruption of the circadian melatonin signal. J Pineal Res 2015; 59:60–9.
105. Xu J, Liu D, Niu H, Zhu G, Xu Y, Ye D, et al. Resveratrol reverses Doxorubicin resistance by inhibiting epithelial-mesenchymal transition (EMT) through modulating PTEN/Akt signaling pathway in gastric cancer. J Exp Clin Cancer Res 2017;36:1–14.
106. Chen J, Zhou C, Li J, Xiang X, Zhang L, Deng J, et al. miR-21-5p confers doxorubicin resistance in gastric cancer cells by targeting PTEN and TIMP3. Int J Mol Med 2018;41:1855–66.
107. Rameshknia V, Movahhedi M, Akhavan A, Majidinia M, Yousefi B. Effect of melatonin on reversing multidrug resistance by targeting phosphatase and tensin homolog in leukemia cancer cells. Iran Red Crescent Med J 2021;23:e212.
108. Kiefer T, Ram P, Yuan L, Hill S. Melatonin inhibits estrogen receptor transactivation and cAMP levels in breast cancer cells. Breast Cancer Res Treat 2002;71:37–45.
109. Sakatani A, Sonohara F, Goel A. Melatonin-mediated downregulation of thymidylate synthase as a novel mechanism for overcoming 5-fluorouracil associated chemoresistance in colorectal cancer cells. Carcinogenesis 2019;40:422–31.