Review

The dual-actions of melatonin as a potential oncostatic agent and a protector against chemotherapy-induced toxicity

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ABSTRACT

Cancer is one of the most complicated and arduous diseases, causing immense physical and emotional tribulations in the life of patients. Carcinogens can lead to genetic mutations and cancer progression either by directly binding to DNA covalently, forming cross-links, or indirectly via the generation of oxidative stress and/or by other recondite mechanisms. Despite being the most widely used treatment, chemotherapy has several adverse consequences, including acute and/or chronic toxicities. Numerous studies have demonstrated melatonin being a potential anticancer molecule with multiple activities including prevention of the initiation, promotion, and progression of cancer. In addition to its role as a potent antioxidant, melatonin exhibits its cytostatic effects by arresting the mutated cell in the G0/G1 phase, preventing epithelial-to-mesenchymal transition and inciting the immune battle against tumours, possibly by dampening MMP activities. Melatonin inhibits the MAP-K/ERK and p38 pathways and regulates NF-κB-mediated inflammatory responses. Melatonin exerts its anti-angiogenic activity by curbing VEGF levels, while its anti-estrogenic activity by inhibiting the cellular uptake of linoleic acid (LA). In addition, melatonin reduces the toxicities of the chemotherapy while improving its effectiveness in cancer treatment. The purpose of this review is to assemble the knowledge available on melatonin's oncostatic role and its protective effects against chemotherapy-induced toxicities. Further studies are needed to investigate the adjunctive role of melatonin with chemotherapy in the clinical setting and to corroborate its effectiveness in cancer cure.

Key words: Melatonin, cancer, chemotherapy, anticancer drug, oncostatic, toxicity

1. INTRODUCTION

Cancer is one of the major causes of death worldwide, and its rising trend will cause serious consequence for premature mortality in the years to come (1). In 2020, it was responsible for approximately 10 million fatalities, with an estimated 19.3 million new cases in both sexes across all cancer types. Among them around 58.3% of cancer fatalities occurred in Asia (2).

Accumulating evidence suggests various risk factors leading to cancer initiation and progression. These include smoking, alcohol abuse, cancer-inflicting viruses, diet, pollution, ionizing and non-ionizing radiation, heavy metals, medicinal drugs, and others (3-5). Besides, several acquired or inherited factors may emerge as prominent aetiologies of cancer (6, 7). Both intrinsic and extrinsic factors are capable of inducing DNA damage. Mutations in genes that have the sustained DNA damage due to impaired repair mechanisms promote cell proliferation and impair apoptosis, causing tumorigenesis (8-11). DNA damage caused by oxidative stress can specifically cause cytosolic chromatin fragments and further aggravates this damage (12). In general, genome instability is a driving force behind intratumor heterogeneity and the progression of cancer (13, 14).

Currently, the main treatments for cancers include radiation, chemotherapy, and surgery. The use of these therapies singly or in combination has limited effectiveness, therefore, identification and development of new cancer-preventive agents are required (15). Classical anticancer therapies like radiotherapy and chemotherapy impact both normal and malignant cells and elicit side effects like nausea, fatigue, vomiting, pain, etc. (16, 17). They also lead to disruption in normal cell-growth signalling and DNA damage which result in organ-specific toxicities and cell death (18, 19).

Melatonin (N-acetyl-5-methoxytryptamine), is a molecule produced principally by the pineal glands in humans and other animals in response to darkness (20). It participates in the regulation of circadian rhythms but also exerts its versatile biological activities including cell cycle regulation, maintenance of mitochondrial function, bone metabolism, reproductive modulation and endocrine homeostasis (21, 22).

Multiple studies have shown the anti-carcinogenic effect of melatonin through its receptor-dependent and independent mechanisms (23). Furthermore, melatonin has shown its potential in ameliorating the toxicity induced by chemotherapeutic drugs while increasing the efficiency of chemotherapy with reducing adverse effects. This therapeutic potential is redolent of melatonin's possible efficiency as an adjuvant of anticancer therapies (24, 25).

This review explores the current knowledge regarding the therapeutic potential of melatonin against cancer as well as reducing the side effects of chemo-therapeutic drugs, while highlighting its potential mechanisms.

2. CARCINOGENS AND CARCINOGENESIS

In early epidemiological studies of cancer, the first recognized carcinogens were associated with certain occupations (26). Yamagiwa and Ichikawa have identified that toxic chemicals are capable of causing cancer directly (27). After being biologically activated to reactive intermediates, environmental toxins have been shown to induce mutations in key genes. These chemicals play a critical role in promoting tumorigenesis by stimulating the proliferation of cells containing oncogenic mutations. Additionally, these chemicals can provoke oxidative damage to cellular macromolecules and disrupt metabolic pathways leading to carcinogenesis (28-31). The term of carcinogens refers to substances that, irrespective of their origin, are capable of causing DNA damage and mutations via several mechanisms, therefore, resulting in cancer development (32-35).These are agents that increase the prevalence of cancer in relevant organisms compared to concurrent and/or historic controls (36). Some common carcinogenic mechanisms include oxidative stress, interactions with cellular receptors, chronic inflammation, immunosuppression, and epigenetic changes such as modifications of histones and cellular structural components (37).

The IARC (International Agency for Research on Cancer) has defined ten key attributes of human carcinogens, and as per their specifications, a carcinogen 1. Can be activated metabolically or is electrophilic; 2. Is genotoxic; 3. Alters DNA repair or disrupts genomic

stability; 4. Promotes epigenetic alterations; 5. Generates oxidative stress; 6. Produce chronic inflammation; 7. Is immunosuppressive; 8. Influences receptor-mediated effects; 9. Results in immortalization; 10. Alters nutrient supply, cell proliferation, and cell death (33, 38-40).

3. MODE OF ACTION OF CARCINOGENS

Cancer pathogenesis involves a complex interaction between extrinsic and intrinsic factors. It usually manifests through an uncontrolled proliferation of genetically altered cells (41). Fieser and others have proposed that carcinogen metabolism plays a critical role in cancer development. These were later confirmed by animal studies conducted by James and Elizabeth Miller (42-46). The study of Omura and Sato revealed that the carcinogenic chemicals are metabolized principally by cytochrome p450s or cyps, which are considered phase I xenobiotic-metabolizing enzymes (47, 31). Furthermore, phase II xenobiotic-metabolizing enzymes (like glutathione-S-transferases, Uridine diphosphate-glucuronosyltransferases, etc.) have also been identified to play a crucial role in the metabolism of carcinogenic chemicals (28). Chemical carcinogens can also lead to polymorphisms in phase I and II xenobiotic-metabolizing enzymes, which have been associated with a modified risk of cancer development (29, 30, 48).

Based on their carcinogenic mechanisms, all carcinogens can be categorized as genotoxic or non-genotoxic one (29). The summary and modes of actions of common carcinogens are described in Table 1.

Table 1: Summary and modes of action of common carcinogens.

CLASSIFICATION OF CARCINOGENIC AGENTS	MODE OF ACTION	REFERENCES
Genotoxic carcinogen	They interact with the genomic DNA of the target cell and damage it, resulting in mutations that are transmitted down to the daughter cells.	(49)
Direct-acting or activation-independent carcinogens	Carcinogens that are capable of producing cancer without being metabolized. They generally exist as highly reactive electrophilic molecules, that directly bind to and interact with DNA and other cellular macromolecules. They frequently lead to tumor formation at the location of their exposure, because of their high reactivity. The Ames mutagenesis bioassay typically detects these carcinogens without additional metabolic activation. Some examples of these carcinogens include Infrared and Ultraviolet radiation, alkylating agents, epoxides, sulphate, and alkyl esters, propiolactone, halo ethers (bis (chloromethyl) ether), halogen derivatives like mustard gasses, imines, nitrosamides, and nitrosoureas, etc.	(50-54)
Indirect-acting or activation-dependent carcinogens	Most DNA-reactive carcinogenic agents possess a procarcinogenic form. The bioactivation of procarcinogens via P450 can lead to the formation of the carcinogen's DNA binding and reactive form. Indirect-acting carcinogens are generally unable to cause cancer at the application site, rather, they are more likely to cause cancer in the tissues that can activate metabolically the procarcinogenic form into its DNA-reactive form. Aflatoxins and polycyclic aromatic hydrocarbons (PAHs) are examples of DNA-reactive indirect-acting carcinogens.	(50, 55-59)

Non-genotoxic or non-DNA reactive carcinogens	Many chemicals can cause cancer through pathways that do not entail the direct binding of chemicals or their metabolites to DNA or bring about heritable genetic changes. Most of the time, non-DNA reactive carcinogens cause tumor formation in tissues that exhibit a high rate of spontaneous tumorigenesis. These agents that work via non-DNA reactive mechanisms are frequently associated with the promotion of the tumor stage of the carcinogenesis process, requiring long-term exposure and relatively high levels for tumour to develop. There are several mechanisms by which they exert their carcinogenic effect-like a2u-globulin binding, sustained cytotoxicity and proliferation of cells, the generation of oxidative stress, and receptor-mediated effects (cytochrome P450 induction, proliferation of peroxisomes), and altered DNA methylation. Examples of non-genotoxic carcinogens include: endocrine modifiers, dichlorodiphenyltrichloroethane (DDT), carbon tetrachloride (CCl4), etc.	(50, 60-62)

In addition to these mechanisms, some alterations in a subset of tumor suppressor genes and proto-oncogenes have been explicitly linked to cancer initiation (46). The SPI-1 (Spi-1 proto-oncogene) transcription factor contributes to cancer progression through the regulation of oncogene transcription (63). Some examples of tumor-suppressor genes are retinoblastoma 1 protein (RB1) and P53. The inactivation or absence of tumor suppressor genes due to mutations leads to cancer (64).

Tissue-specific alterations are also elicited by some hormonally active agents like steroids, peptide hormones, and biogenic amines that interact with selective receptors to exert such alterations. Trophic hormones have been shown to cause cell proliferation in the organs they target to. When hormonal regulatory mechanisms are compromised, certain hormones display a persistent hike in their circulatory levels. Such activities may contribute to tumor development. The development of ovarian neoplasms by decreasing estradiol levels and increasing luteinizing hormone levels, as well as, in rats, the initiation of thyroid tumors by phenobarbital-type P450 inducers, are two well-studied examples (46, 65, 66).

4. ANTICANCER AGENTS

Chemotherapy, which involves the use of low molecular weight drugs, is among the most effective cancer treatments available, and the search for new drugs persists along with conventional therapeutic practices (67, 68). During the 1940s, the utilization of chemotherapy was initiated with nitrogen mustards, which are incredibly potent alkylating agents, and antimetabolites. Because of the early success of these initial strategies, an enormous number of other anticancer medications have been developed (69). Currently, with the increasing prevalence of cancer, cytotoxic drug treatments are gaining popularity, and these therapeutic approaches are capable of completely curing some cancers. However, the success of cancer treatment varies greatly depending on the types of cancers and the stages of diagnosis (70, 67).

Conventional Anticancer agents are categorized based on their mode of action and include DNA-interactive agents like alkylating agents (such as cyclophosphamide), microtubular poisons (e.g., paclitaxel), antimetabolites (like 5-fluorouracil [5-FU]), topoisomerase inhibitors (such as irinotecan), hormones, molecular targeting agents, cytotoxic antibodies (e.g., bleomycin), and other biological agents (71,72).

The main objective of chemotherapy is to prevent the proliferation of tumours, thereby averting invasion and metastasis. However, chemotherapy can damage healthy cells (73). Although traditional cytotoxic antineoplastic drugs, particularly platinum-based drugs like carboplatin, oxaliplatin, and cisplatin have achieved major success over the past decades,they

generally have narrow therapeutic windows. This was primarily attributed to their high toxicity, lack of tumor specificity, poor water solubility, and the possibility of inherent and acquired drug resistance. All these have severely limited their use (74-79). Other frequently clinical used anticancer drugs including paclitaxel, fluorouracil, and doxorubicin also exhibit similar limitations (76). These drugs also foster acute and long-term side effects, which may be reversible and irreversible (80). The toxic effects of some anticancer drugs on different tissues have been discussed in detail in Table 2. Such adverse toxicities not only limit the therapeutic potential of anticancer drugs but also decrease the rate of survival and quality of life of cancer patients. Thus, the demanding for new anticancer agents, which are more efficacious and less toxic was urgently required (76).

Table 2: Summary of classic anticancer drug-induced organ toxicities.

ANTICANCER DRUG-INDUCED ORGAN TOXICITY	CONSEQUENCES	REFERENCES
Hematological toxicity	Chemotherapywith carboplatin, cyclophosphamide, melphalan, etc. may jeopardize activity of proliferating haematopoietic precursor cells, resulting in the depletion offormed elements, and causing life-threatening infections and hemorrhages. Peripheral cytopenia due to the suppression of the bone marrow is a frequently observed chemotherapy side effect that can lead to acute and chronic marrow destruction. Cyclophosphamide has been reported to alter hematopoietic factors, leading to myelotoxicity.	(81-84)
Cardiotoxicity	Cardiotoxicity is known to be caused by anthracenediones and alkylating agents. ROS-mediated oxidative damage lies at the core of these drug-mediated cardiotoxicities. Both prostate and breast cancer drugs are included in cardiotoxicity warnings on Some drugs can lead to cardiotoxicity by inhibition of mitochondrial protection pathways. Taxanes are responsible for the prolongation of the QT interval, leading to atrial fibrillation and bradycardia. Damage to cardiomyocytes and necrosis caused by thromboembolism and vascular damage are reported during alkylating drug usage.	(85-89)
Gastrointestinal toxicity	The side effects of GI like nausea, bloating, vomiting, constipation, ulceration, and particularly diarrhea caused by chemotherapy are major hurdles resulting in delays, reduction of doses, and cessation of treatment in many cancer patients. Mucositis, which involves inflammation and loss of epithelial cells in the barrier lining of the GI (gastrointestinal) tract, is one of the most severe side effects of chemotherapy. Stomatitis, diarrhea, dysphagia, oesophagitis, proctitis with pain and bleeding, and oral ulceration arise from chemotherapy. The most commonly used anticancer agents for colorectal cancer, such as 5-fluorouracil, cisplatin, oxaliplatin and irinotecan are linked with mucositis and gastrointestinal dysfunction.	(90-97)

Neurotoxicity	The neurotoxicity caused by vinca alkaloids (vindesine, vincristine, and vinblastine) may be dosage dependent and includes peripheral, autonomic, and cranial neurotoxicity. Classic anticancer agents including doxorubicin, paclitaxel, cisplatin and current anticancer agents like bortezomib and trastuzumab can cause peripheral neuropathy. Several studies have demonstrated that chemotherapy can cause short and long-term mood changes as well as cognitive deficits, including impairment in learning, attention, and concentration, speed of information processing, short-term and working memory, and executive decisions (like decision-making, multitasking, language) Oxaliplatin can cause tight junction disassembling and brain dysfunction in the endothelial cell line (RBE4) of rat brains.	(98-102)
Nephrotoxicity	Another vital side effect is nephrotoxicity since many patients receiving chemotherapy present impaired renal function. The activation of the p53, DNAase 1, and MAP kinase pathways, as well as the increase in TNF-α are involved in cisplatin-induced nephrotoxicity. Cyclophosphamide causes hemorrhagic cystitis, which is closely associated with hyponatremia. Nephrotoxicity has also been reported with biologics like cetuximab and bevacizumab. Bevacizumab can cause proteinuria via immune complex-mediated focal glomerulonephritis, and hypomagnesemia is caused by cetuximab by inactivating the TRPM6 magnesium channel. Essentially, both biologics and small molecules impair renal excretion by affecting glomerular perfusion and vasculature, resulting in nephrotoxicity. There have been reports of renal failure, which may be to some extent attributed to rhabdomyolysis, associated with the use of a marine-derived alkylating agent, trabectedin for treating advanced sarcoma of soft tissue.	(103-105)
Hepatotoxicity	The most commonly used antimetabolite, methotrexate, has been linked to hepatotoxicity through the activation of inflammatory pathways, ROS generation, and cytokines. Peroxidation of membrane lipids and disruption of mitochondrial energy metabolism induced by doxorubicin can also lead to liver damage. Fatal hepatotoxicity along with severe reactions has been caused by Imatinib.	(103, 106, 107)

5. MELATONIN, AS AN ONCOSTATIC AGENT

In 1958, Aaron Lerner discovered and isolated melatonin from the bovine pineal gland (108). The pineal gland secretes melatonin as its primary hormone. Extrapineal sources of melatonin include the bone marrow cells, retina, skin, platelets, Harderian gland, lymphocytes, cerebellum, and particularly the digestive tract of vertebrates (109). Melatonin is produced not only in animal tissues but also in plants and their derivatives. Melatonin has been identified in wine, olive oil, tomatoes, beer, and juices. Darkness is a prerequisite for pineal melatonin synthesis and its secretion has circadian and in seasonal rhythms regulated via the light-sensitive retino-pineal pathway (110).

Melatonin exerts multiple effects, both through receptor-independent and receptor (MT1 and MT2)-dependent mechanisms (111-114). It is well known for its antioxidant and anti-

inflammatory properties, and its effect on sleep-wake cycles, metabolism, and reproduction. The effects of melatonin on cancer have been investigated extensively in recent decades identifying its anti-proliferative, anti-oxidative, pro-apoptotic, cytotoxic, and differentiative activities, as well as its potential to modulate epigenetic processes in cancer cells (110).

6. MELATONIN AS AN ANTIOXIDANT

An imbalance between the production and elimination of free radicals results in oxidative stress (115, 116). In addition to DNA damage, oxidative stress causes damage to other macromolecules, which also contributes to tumor development and progression (117). Furthermore, excess free radicals can disrupt intercellular signalling linked to tumorigenesis (116). Several mechanisms are responsible for the antioxidative function of melatonin, including its direct role as a free radical scavenger, the enhancement of activity of antioxidant enzymes and their gene expression, and the suppression of pro-oxidant enzymes. To preserve mitochondrial function and chelating $Fe^{2+/3+}$ to inhibit harmful Fenton reaction are also the mechanisms of melatonin to reduce ROS production (118). In addition to protecting DNA from oxidative damage, melatonin maintains genomic stability (119). It also regulates oxidative stress by impeding the NF-κB pathway (120). It's noteworthy that melatonin's antioxidant activity is conditional regarding the reduction of oxidative stress. Under certain circumstances, such as in malignancies, melatonin may paradoxically play the role of a pro-oxidant, causing cell death by apoptosis (121).

7. MELATONIN IN THE INHIBITION OF TUMOR PROGRESSION

Melatonin is capable to inhibit the proliferation of neoplasms via cytostatic and cytotoxic mechanisms, making it an effective antitumor agent (122). The cytostatic action of melatonin was demonstrated in a breast cancer cells, MCF-7 cells. In these cells, melatonin restrains them in the G0/G1 phase or delays their transition to the S phase of the cell cycle (122-124). The inhibitory effect of melatonin on proliferation of ovarian cancer cells (OVCAR-429) was also observed in a dose- and time-dependent manner when the cells were incubated with melatonin (at a concentration of 400-800 μM) for 24-72 h (125).

Melatonin has been demonstrated to have anti-metastatic properties in some types of cancer, specifically by preventing EMT (epithelial-to-mesenchymal transition) (126). Melatonin significantly reduces MAP-K/ERK signalling activity, which is regulated by the human epidermal growth factor receptor 2 (HER2) known for promoting human breast cancer cell invasion and metastasis (127, 128). Melatonin's anti-invasive effect may be attributed to its suppression of the p38 pathway and down-regulation of metalloproteinases-2 and -9 activity and expression (129).

The antitumor properties of melatonin including the potential to induce apoptosis, an effect observed only in cancer cells lead to a substantial reduction in the volume of cancer and an improvement in patient health (15, 130-132). In cultured human adenocarcinoma cells treated with melatonin, caspase 3 activity was increased, the expressions of Bax and p53 were up-regulated but Bcl-2 was down-regulated (133).

8. ANTI-ANGIOGENIC EFFECT OF MELATONIN

The process of angiogenesis involves the formation of new blood vessels and is crucial to wound healing, embryonic development, and carcinogenesis. Tumors that lack vascular support are prone to necrosis and even apoptosis (134). In both normal and malignant cells, VEGF (vascular endothelial growth factor) is essential for new blood vessel development and

for promoting angiogenesis. VEGF has three key receptors: VEGF-1, 2, and 3. However, its main function is mediated via VEGF-1(135-138). Declining circulating VEGF levels in serum correlate with the strong response seen in patients with static-metastatic cancers (139).

Melatonin inhibits HIF-1α (Hypoxia-inducible factor 1-alpha) in prostate cancer cells by suppressing the translation of proteins (140). Importantly, melatonin, supresses tumor growth by inhibition angiogenesis but in normal cells it stimulates angiogenesis to promote wound healing (141).

9. EFFECT OF MELATONIN ON THE IMMUNE SYSTEM

Numerous studies have shown a strong association between the immune system and melatonin (142-145). Melatonin can regulate cytokine production and immune cell proliferation via its receptors present in immune cells (146, 147). Melatonin can restore impaired T-helper cell activity, modulate lymphocytes, induce the proliferation of T-lymphocytes, protect CD4+ T-cells against apoptosis, and prevent the apoptosis of B-cell precursors in the bone marrow (148). It triggers the generation of IL-2, IL-10, IL-6, IL-12, and IFN-γ in mononucleated cells, resulting in a TH-1 lymphocyte response (149). It stimulates the activity of natural killer cells in humans as well as increases the antitumor properties of the immune system (150). Liu *et al*. found that melatonin suppressed the regulatory T cells (Tregs) in mice bearing gastric cancer tumors, leading to cell death (151).

10. MELATONIN'S ANTI-ESTROGENIC PROPERTIES AND INHIBITION OF LINOLEIC ACID UPTAKE IN CANCER CELLS

Numerous investigations have revealed that estrogen is critical to the proliferation of neoplastic breast epithelium (152-154). Estrogen receptor expression increases as cancer progresses (154, 155). Studies have demonstrated that melatonin reduced the proliferation of breast cancer by inhibiting estrogen receptors (156, 157). Moreover, treatment with melatonin inhibited the proliferation of human breast cancer stem cells by down-regulating the transcription factor OCT4 and estrogen receptor-a (158).

In addition to its interactions with estrogen, melatonin decreases linoleic acid (LA) uptake, a crucial component essential for the initiation of the cellular pathways linked to hormone-dependent malignancies of the breast (159).

11. EPIGENETIC ACTIONS OF MELATONIN

The ability of melatonin to switch genes on and off can aid in controlling epigenetic regulations. For instance, melatonin can control transcription factors that are affected by inflammatory and nitro-oxidative conditions (159). Inflammation is caused by pathways governed by the family of activator protein-1 (AP-1) and NF-κB. These pathways directly lead to the activation of pro-inflammatory mediators and cytokines such as interleukins, TNF-α, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), and cytokine-inducible nitric oxide synthase (iNOS). The activation of these transcription factors triggers epigenetic modification via altering the chromatin's structure, either by acetylating histones or by methylating DNA (160). According to numerous studies, melatonin selectively suppresses COX-2, iNOS and MMPs resulting in the inhibition of NF-κB (161-163). The schematic diagram (Figure 1) shows the potential role of melatonin as an oncostatic molecule.

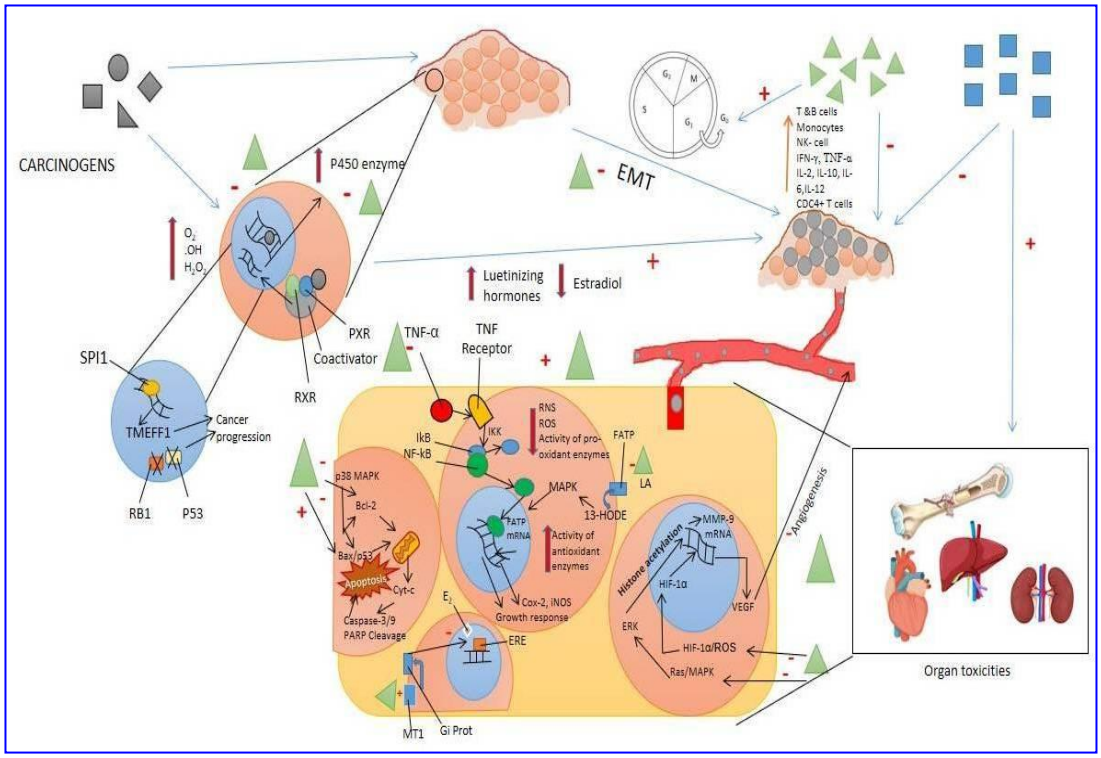

Fig. 1. The potential roles of melatonin as an oncostatic molecule.

Carcinogens can lead to cell mutation and cancer formation and progression either directly by binding with DNA to form DNA cross-links or indirectly by the generation of free radicals and induction of the Cytochrome P450 enzyme. Tumor suppressor genes (RB1 and P53) and oncogenes (SPI-1) along with increased levels of luteinizing hormone and decreased levels of estradiol contribute to cancer development.Melatonin, in addition to its role as a potent antioxidant, exhibits cytostatic effects by arresting the mutated cell in the G0 or G1 phase or delaying its transition to the S phase. It also prevents epithelial-to-mesenchymal transition. Melatonin is also involved in the upregulation of the immune system. It significantly suppresses the Mapk/ERK and p38 pathways and regulate the NF-κB pathway. Melatonin exerts its anti-angiogenic properties by curbing VEGF levels. It also exhibits anti-estrogenic properties and inhibits LA uptake by the cells.

Green triangle: melatonin, Blue box: anticancer drugs, PXR: Pregnane X Receptor, RXR: retinoid X receptor, TMEFF1: Transmembrane Protein with EGF-like and 2 Follistatin-like domains 1, FATP: Fatty acid transport proteins, ERE: estrogen response element, E_2: estradiol, 13-HODE: 13-Hydroxyoctadecadienoic acid, Ras: rat sarcoma

12. THE ROLE OF MELATONIN IN THE PREVENTION OF ANTICANCER DRUG-MEDIATED TOXICITY

Melatonin's oncostatic and immunomodulatory properties support its use in conjugation with conventional anticancer treatment (164). Melatonin and classic chemotherapeutic drugs as a chemohormonotherapeutic combination are further substantiated by its ability to lower the toxicity of anticancer drugs (165). The multifaceted role of melatonin in mitigating various anticancer drug-induced toxicity is discussed in Table 3.

Table 3: Summary of the preventive role of melatonin against toxicities of various anticancer drugs.

TOXICITY INDUCED BY ANTICANCER DRUGS	PREVENTIVE ROLE OF MELATONIN	REFERENCES
ANTHRACYCLIN-INDUCED TOXICITY	Melatonin exerted cardioprotective effects against damage induced by doxorubicin in rats, by decreasing ST segments elevation, increasing the R-amplitude, reducing serum levels of cardiac injury markers, protecting the activity of antioxidant enzymes, decreasing lipid peroxidation, and modifying serum lipid profile. Melatonin, when given with daunorubicin, decreased the proportion of apoptotic cardiomyocytes and suppressed nitrosative stress induced by epirubicin.	(166-168)
PLATINUM DRUG-INDUCED TOXICITY	Melatonin inhibited cell death induced by cisplatin and increased the expression of antiapoptotic Bcl-2 gene and protein while decreasing levels of phosphorylated apoptotic protein p53, Bax, and cleaved caspase 3 and also significantly reduced cisplatin-induced DNA fragmentation and renal cytotoxicity. Melatonin protected against peripheral neuropathy induced by oxaliplatin. Melatonin reduced the levels of mitochondrial lipid peroxidation and protein carbonyl content induced by oxaliplatin and controlled the alterations in mitochondrial enzymatic and non-enzymatic antioxidants as well as complex respiratory enzymes. In preclinical and clinical studies on neuroinflammatory pain, melatonin exerted antiallodynic and anti-inflammatory effects.	(169-172)
ALKYLATING AGENT-INDUCED TOXICITY	Melatonin exerted anti-inflammatory effects mitigated toxicity induced by alkylatingagentsvia the mechanism of inhibition of iNOS and scavenging peroxynitrite. Melatonin had powerful antigenotoxic effects and inhibited chromosomal aberrations induced by cyclophosphamide toxicity in mice, possibly by the elevated antioxidant status by melatonin. Melatonin may also ameliorate the spermatological toxicity induced by busulfan in male patients.	(173-177)
ANTIMETABOLITES-INDUCED TOXICITY	Pretreatment with melatonin reduced methotrexate-induced oxidative stress, altered antioxidant enzyme activity, and increased the activity of myeloperoxidase, implying that melatonin might reduce renal damage through anti-inflammatory and antioxidant actions. Melatonin also alleviated the cognitive defects which were the result of 5-fluorouracil-induced hippocampal neurodegeneration.	(178-180)
MITOTIC INHIBITORS-INDUCED TOXICITY	Melatonin treatment during taxane chemotherapy was associated with a lower occurrence of peripheral neuropathy. Melatonin reduced mitochondrial damage and neuropathic pain caused by paclitaxel.	(181)
MOLECULAR TARGETED ANTIBODIES-INDUCED TOXICITY	The humanized monoclonal antibody trastuzumab targets the extracellular domain of HER2 and is used in HER2-positive breast cancer patients as a crucial part of adjuvant treatment and metastasis therapy. Nonetheless, its serious side effects restrict its use. The levels of serum CK-MB and oxidative stress markers	

	were highly increased following trastuzumab treatment; melatonin administration reversed these changes, returning them close to normal levels, implying that melatonin is beneficial in reducing cardiotoxicity induced by trastuzumab.	(182-184)

13. MELATONIN AS A POTENTIAL ADJUVANT THERAPEUTIC IN CANCER TREATMENT

Several studies have examined the effectiveness of melatonin as an anticancer treatment in combination with chemotherapy in cancers such as cervical, breast, colon, lung, hematological, hepatic, and others (185). Melatonin exerts a range of anticancer properties at various stages of tumor progression and metastasis (186). Furthermore, melatonin in conjugation with chemotherapies not only increased the efficacy of anticancer drugs (187-189) but improved the cancer-related symptoms like cachexia, delirium, and insomnia (110).

This indoleamine can also enhance the anticancer activity of doxorubicin by preventing its outflow from cancer cells mediated by P-glycoprotein (190)**.** In the MCF-7 human breast cancer cells, doxorubicin and melatonin in combination were more effective in eliciting apoptosis, depolarization of the mitochondrial membrane, and activation of caspase 3 and caspase 9 than doxorubicin alone (191). It promotes cisplatin-induced cell cycle arrest and apoptosis in human lung adenocarcinoma cells (192). Melatonin significantly enhanced the activities of 5-fluorouracil to inhibit colon cancer cell proliferation, formation of colonies, cell migration, and invasion. Melatonin and 5-fluorouracil synergistically induced cell cycle arrest via caspase/PARP-dependent apoptosis pathway activation (193). Melatonin also enhanced paclitaxel's antitumor effects in the endoplasmic reticulum of endometrial cancer cell line expressing MT1 receptor (25).

Melatonin at a dose of 20 mg/day orally in combination with chemotherapy increased the survival of patients by 1 year and potentiated tumor regression (194). Another study showed that combination of etoposide cisplatin and melatonin had a 6% chance of survival rate after five years, whereas no patients survived who received etoposide and cisplatin only (195). Melatonin, when combined with radiotherapy, increased the survival rate by 153.5 months as compared to 64.0 months in patients without melatonin co-treatment (196). Furthermore, it significantly reduced myelosuppression, and neuropathy, indicating a better tolerance to chemotherapy for patients treated with anticancer drugs (197).

14. EMERGING ROLE OF MELATONIN IN THE MODULATION OF TUMOR MICROENVIRONMENT

Recent work indicates that the melatonergic pathway is present in all cells of humans, primarily mitochondrial melatonergic pathway is proposed to be a significant target of tumor fluxes in the tumor microenvironment (198, 199). Notably, the melatonergic pathway does not always control the production of melatonin but, regulate the N-acetylserotonin (NAS)/melatonin ratio, including from the pineal gland at night (200). Melatonin can be 'backward' converted to NAS by a number of factors, including the aryl hydrocarbon receptor (AhR)-induced cytochrome P450 (CYP)1A2 and CYP1b1 (201). As tumor-induced kynurenine release activates the AhR to modulate immune responses in the tumor microenvironment, AhR activation is an important aspect of tumor microenvironment pathophysiology, including via AhR-induced NAS (202). NAS, a brain-derived neurotrophic factor (BDNF) mimic can activate the BDNF receptor, tyrosine receptor kinase B (TrkB) (203). This would indicate that an increase in NAS/melatonin ratio may be of importance to tumor

survival, that is, AhR activation stimulates TrkB activity to increase the proliferation and survival of cancer stem-like cells (204).

Regulation of tumor initiation and pathophysiology by melatonin may be partly mediated via its uptake by mitochondria via the peptide transporter (PEPT)1/2 and the organic anion transporter (OAT)3 (205-207). Melatonin not only has antagonistic interactions with the AhR, but can also induce the mitochondrial melatonergic pathway in cells of the tumor microenvironment, thereby altering the intercellular 'homeostatic' interactions of cells in the tumor microenvironment (208). The intercellular interactions of melatonin on tumor microenvironments with relevance to both the pathoetiology and physiology of cancer is required for further investigation.

15. SUMMARY AND CONCLUSION

An array of studies has looked into the melatonin as a powerful salutary molecule with diverse biological activities including oncostatic, anti-oxidative, immunomodulatory, and anti-inflammatory properties. Results from these studies have shed light to use melatonin as a potential adjuvant of chemotherapy (209,210).

Melatonin reduces the interaction of carcinogens with DNA and decreases the oxidative stress caused by carcinogens. Melatonin also protects against damage to cellular macromolecules and other elusive mechanisms. The antitumor effects of melatonin are amplified by its activities blocking cell proliferation, enhancing tumor apoptotic pathways, strengthening the immune system, and suppressing angiogenesis. In addition, melatonin reduces toxicities of various antineoplastic drugs on normal cells, therefore, enhances the tolerance of patients to chemotherapy.

This review explores melatonin's potential as an adjuvant in combination with chemotherapy for improving survival and quality of life for cancer patients. Further studies are required to unravel the clinical outcomes of melatonin as an adjuvant with classic anticancer drugs. Furthermore, mechanisms of melatonin in mitigating the toxicities of anticancer drugs should be further explored. In conclusion, our review encourages further research and clinical trials to identify the effectiveness of melatonin in inhibiting carcinogens, checking cancer development, and ameliorating toxicities induced by anticancer drugs. Understanding the underlying molecular events will present a clear picture of the mode of action of melatonin, and its role as a potential adjuvant in cancer therapy will obtain greater recognition.

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AUTHORSHIP

The concept of the review article was developed by Dr. DB, Dr. AC, SS and SC. Moreover, SC and SS contributed in drafting the manuscript, prepared the figures, and edited it. Dr. DB and Dr. AC revised the manuscript critically and finally approved it.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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