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## The promising oncostatic effects of melatonin against ovarian cancer

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### Abstract

Melatonin (MLT) is a pineal hormone, secreted at the subjective night. It regulates many physiological activities, including the sleep-wake cycle, gonadal functions, free radical scavenging, immunomodulation, neuro-protection, and cancer progression. Melatonin acts through cell surface receptors (MT1 and MT2) as well as nuclear receptors. Circadian dysfunction can alter the secretion of melatonin. Inappropriate melatonin level promotes the initiation of many pathologies including cancer. Ovarian cancer (OVC) is a common form of gynecological disease. Several studies indicate the profound link between impaired melatonin secretion and the progression of ovarian cancer. Melatonin exerts oncostatic effects in multiple ways; it acts as a potent antioxidant, induces apoptosis, and regulates metabolism, and chronic inflammatory response in ovarian cancer cells. Moreover, melatonin improves the efficacy of the current treatment regimen of ovarian cancer and can be used as an adjuvant.



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### Introduction

Melatonin (MLT), an endogenous iodolamine, called hormone of darkness is released from the pineal gland [1]. The highest peak of MLT arises at 2 a.m; it transfers a signal of darkness to all the cells [2,3]. It has a crucial role in maintaining the internal milieu and makes synchronization with circadian rhythm, and neuroendocrine functions [4,5]. MLT acts as a chronobiotic agent as well as a sleep-promoting factor, immune regulator, and jet lag problem reducing agent [6]. Besides these, it has anti-carcinogenic functions by modulating the estradiol synthesis, cell cycle regulation, induction of apoptosis [7,8] as well as anti-angiogenic effects, antioxidant properties, and immune cell regulation through several cytokines production [3,8]. MLT is considered a potent natural anti-tumor hormone; an elevated level of this hormone decreases the risk of development of a variety of cancer in different tissues, including the ovary. A retrospective study conducted by Chen et al. [9], reported that melanin concentrations are low in females with ovarian cancer (OVC) compared to normal women (41.8 versus 82.4 pg/mL). Several studies reported that MLT has effective therapeutic capacities against OVC [3]. Supplementation of MLT for 60 days to the women having OVC had revealed that MLT significantly reduced the ovarian tumor mass and cancer risk [10].

OVC is one of the most common causes of the high rate of morbidity related to gynecological malignancy that rank 3rd after cervical and uterine cancer [11]. Light exposure on retina suppresses the pineal MLT synthesis and release [12]. In 1978, Cohen et al. [13] hypothesized that the improper functions of

the pineal gland was associated to breast cancer and later they revealed that MLT suppresses the activity of pituitary gonadotrophic hormones. Several reports had indicated that the women working in the night shift were facing irregular menstrual cycles, infertility disorder, and failure to pregnancy due to disruption of gonadal hormone levels [14,15]. Animal studies also reported that nocturnal MLT levels directly influence anti-proliferative and anti-metastatic effects on OVC cells [16,17]. Some molecular signaling mechanisms like a chronic inflammatory response, oxidative stress (OS), apoptosis, and angiogenesis are associated with the development of OVC [3]. Chemotherapy is the first-line treatment for OVC, co-administration of carboplatin and paclitaxel is mostly applied [18] but recurrence and eventual resistance are common [19]. Recently developed chemotherapies that act as the PARP inhibitors, checkpoint inhibitors, anti-angiogenic agents are blended with conventional chemotherapeutic agents for clinical trials [20]. Despite this, the use of neoadjuvant chemotherapy (NACT) is increasing recently, but the treatment of high-grade serous (HGS) ovarian carcinoma remains at the bottom level [21]; data had revealed that the overall cure rate of OVC remains ~30% [22]. Recent clinical trials advance the therapeutic scenario of ovarian carcinoma after establishment of the role of MLT in the improvement of treatment strategy, cancer prevention and enhancement of the activity of chemotherapeutics [3]. This review has focused on the multidimensional effects of MLT against the progression of OVC and its possible use in cancer treatment.

### Pathogenesis of ovarian cancer

Although, the reasons of OVC still uncertain, several assumptions have been developed: i) "Incessant ovulation hypothesis" was postulated by Dr. Fathalla [23] that is causative of ovarian carcinogenesis. This hypothesis reported that chronic rupture and repair caused by the cyclical ovulatory process was ultimately tumorigenic. Dr. Fathalla also proposed that the ovarian surface epithelium undergoes a malignant transformation as a result of the increasing of DNA abnormalities during follicular growth and ovulation. ii) The second hypothesis is the "gonadotrophin theory" proposed by Cramer and Welch [24]. This hypothesis suggested that gonadotrophins advance the multiplication of ovarian epithelial cells, resulting in the formation of a tumor. iii) Another hypothesis is "hormonal influences [25], which indicated that hormonal effects of progesterone and androgen promote excessive multiplication of the ovarian epithelial cells in the ovaries causes cancer. The peritoneal lining of the ovarian epithelium surface is challenged by inflammatory agents that exist in the peritoneal cavity. Ovulation is the prime physiological function of the ovary, which has pro-inflammatory features [26]. Various factors like chemokines, cytokines, interleukins (IL), tumor necrosis factors (TNF), prostaglandins, plasminogen activators, collagenases, some growth factors (GF), and different immune cells are involved during the ovulatory period that activates pro-inflammatory cascade after immediate release of the ovum [27]. Additionally, some pro-inflammatory molecules like IL-8, CCL2/MCP-1 and CCL5/RANTES increase during the ovulation period [28]. Thus, the induction of inflammatory response along with other physiological factors advance the development of OVC [27,29,30]. On the other hand, increasing levels of estrogens and androgens stimulate inflammation-inducing cells and inductive molecules leading to activate the immune system [31,32]. Activation of inflammatory mediators constantly increases genomic instability [3,33].

### Melatonin and ovarian cancer: molecular mechanisms

Circadian rhythm disruption is associated with greater a risk factor for several diseases, including cancer. Large epidemiological studies have provided strong evidence regarding such a relationship [34-36]. Aspects of modern lifestyles, such as light pollution and light-at-night (LAN) cause intense disruption of circadian rhythms. In the condition of OVC, MLT shows anti-cancer properties in both *in vitro* and *in vivo* studies. The cell lines of OVC exposed to high doses of MLT showed the decreasing effect of cell viability in both dose and time-dependent manner [37,38] MLT was able to decrease the cell viability proliferation and invasiveness of the SKOV3 through the receptor-mediated way [39]. The treatment of MLT leads to the decline levels of several proteins of signaling pathways that are involved in cell cycle regulation, proliferation, OS, inflammation, and apoptosis [3]. Furthermore, MLT decreases the expression of genes related to the epithelial-to-mesenchymal transition (EMT) for the migration of cancer stem cells [40,41]. Other factors like matrix metalloproteinases (MMPs) engaged in the invasiveness of cancer cells. It is associated with extracellular matrix

remodeling capacity [42,43]. Supplementation of MLT downregulates the isoforms of both MMP-2 and MMP-9 in the OVC cell lines [44]. The cell proliferation of OVCAR and PA-1 cell lines was inhibited by MLT by arresting the cell cycle [45,46]. The frequency and size of tumors of the DMBA-induced OVC in rats were decreased by MLT treatment through the reduction of Her-2, pAKT, and mTOR [45,47].

Melatonin positively impacts on E-cadherin levels during cancer in ovary. E-cadherin is a vital constituent of adherent junctions that suppresses cancer progression [48]. Up-regulation of E-cadherin expression has a prognostic value to determine the stage of ovarian tumor [49,50]. The estrogen receptor  $\alpha$  (ER $\alpha$ ) (nuclear receptor) modulates cell homeostasis, proliferation, and differentiation in different tissues. Continuous exposure to estrogen/estradiol (E2) enhances the growth of tumor in ovary [3,51]. MLT suppresses ER $\alpha$  and plays a key role in anti-cancer properties by controlling the ER pathway in cancer cells [52].

### Melatonin as an antioxidant

Melatonin is a potent endogenous free-radical scavenger [53,54]. It scavenges numerous free radicals and reactive oxygen species (ROS), including the superoxide anion (O<sub>2</sub><sup>-</sup>), hydroperoxyl radical (HO<sub>2</sub><sup>•</sup>), alkoxy radical (RO<sup>•</sup>), hydroxyl radical (<sup>•</sup>OH), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), singlet oxygen, (<sup>1</sup>O<sub>2</sub>) peroxy nitrite anion (NO<sub>3</sub><sup>-</sup>), singlet oxygen (O<sub>2</sub><sup>-</sup>) and nitric oxide (NO) [55]. In addition, it was reported that MLT stimulates several antioxidant enzymes, including glutathione reductase, glutathione peroxidase, glucose-6-phosphate dehydrogenase, and superoxide dismutase [54,56-58]. Conversely, it prevents peroxy nitrite levels by the depressing activity of nitric oxide synthases (iNOS, nNOS) and thereby decreasing NO levels [59]. Melatonin protects the membrane lipids and chromosomal DNA from oxidative damage. MLT indirectly removes a variety of toxic free radicals and reactive intermediates and protects the macromolecules from free radical-mediated damage [60,61]. MLT can cross the placenta, blood-brain barrier, and has shown effective antioxidant activity [62]. MLT also exhibits pro-oxidant properties in cancer cells [63]. It triggers the activity of ROS in pre-ovulatory follicular fluid [64].

### Role of melatonin in apoptosis

Melatonin regulates apoptotic response in different types of cancer cells by several mechanisms [65]. Caspases are IL-1 $\beta$ -converting enzyme superfamily, which is an aspartate-specific cysteine proteases. These enzymes play crucial roles to regulate the effective functions of apoptotic signals [66]. In the case of OVC, the expression of caspase-3 is accelerated [67] whereas MLT suppresses the activation and overexpression of this enzyme [68]. Several studies proposed that MLT treatment accelerates apoptosis by enhancing the p53 levels, which is a tumor suppressor protein in cancer cells, including ovary [69]. The study on the different carcinoma cell lines had reported that p53 arrests the cell cycle or induces apoptosis by blocking the G2-phase of the cell cycle [9]. The p53 markedly interacts with some proteins that are engaged essentially in tumor cell maintenance and thereby deactivate them [70]. MLT accelerates the activation of p53 and consequently stimulates apoptotic response in many cancers such as the breast,

prostate [7], colon [71], and the uterus. [72]. Bcl-2 and BAX are two important factors that are related to apoptosis [73]. MLT stimulates the expression of BAX while downregulates the synthesis of anti-apoptotic Bcl-2 [74,75]. Several studies reported that MLT acts as an apoptosis-inducing agent in OVC cells by triggering the release of BAX and lowering the Bcl-2 expression [69,76].

### Melatonin as an anti-inflammatory agent

Despite antioxidant properties, MLT is also an immune modulator that shows both pro- and anti-inflammatory actions. Pro-inflammatory actions are well documented by isolated cell culture studies or in leukocyte-derived cell lines. This action increases the preventive measures against pathogens [77]. MLT influences the secretion of IL-2, IL-10, and interferon- $\gamma$  (IFN- $\gamma$ ) for the activation of the T-helper cells (Th) [78]. Th cells have an oncogenic role. Nuclear factor-kappa B (NF- $\kappa$ B) increases ROS production that leads to instability of the DNA [79,80]. In OVC etiology, NF- $\kappa$ B is an important factor for inflammation [81]. MLT decrease the NF- $\kappa$ B phosphorylation, resulting in the decrease of ROS production [82]. Several research studies reported that the expression of cyclooxygenase-2 (COX2) is high in cancer cells. MLT lowers the action of COX2 [83-85] leading to restriction of the inflammatory response as well as DNA damage [86]. This indolamine also suppresses H<sub>2</sub>O<sub>2</sub>-induced OS by regulating the Akt/ERK/NF $\kappa$ B signaling pathway [87]. It was reported that MLT therapy downregulates the expression of mRNA of the NF- $\kappa$ B1 and NF- $\kappa$ B2 in mice [88]. Furthermore, it also reduces the expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), an important inflammatory cytokine. Collectively, MLT shows defense against inflammatory properties [3,89]. The pro-inflammatory agent TNF- $\alpha$  induces pathological conditions such as chronic inflammation and malignancy [90]. The levels of expression of TNF- $\alpha$  are elevated in OVC cells [91]. Administration of MLT significantly restricts the elevation level of TNF- $\alpha$  in OVC cells. In addition, HER-2 also initiates inflammatory response and tumorigenesis. It initiates the release of IL-1 and IL-6 that triggers NF- $\kappa$ B and STAT3 signaling activities that promote the chemoresistance capacity of the cancer cells and advances metastatic activity [92]. MLT crucially inhibits mesenchymal-epithelial transition to block the invasiveness or metastatic effect [93].

Melatonin also downregulates the Her-2 system by depressing the expression of Her-2 in invasive tumors [17]. The transforming growth factor- $\beta$  (TGF- $\beta$ ) plays a vital role in OVC [94]. Actually, TGF- $\beta$  may increase cell survival by regulating the cell cycle positively and also inhibits apoptosis [95]. The expression of TGF- $\beta$ 1 and its receptors positively influence the growth of tumor cells [96]. MLT attenuates TGF- $\beta$ 1 expression in epithelial cells of OVC [97].

### Effect of melatonin on angiogenesis

Angiogenesis is a vital step in cancer pathology [98]. Angiogenesis is the most important part for solid tumor to meet the oxygen and nutrient supply as well as waste removal [99]. Vascular endothelial growth factor (VEGF) is highly expressed in the patients suffering for cancer [98,100]. VEGF prevents apoptosis of endothelial cells, maintains vascular growth, accelerates cells proliferation, and survival resulting in

progression of carcinogenesis [101]. MLT inhibits angiogenesis by lowering VEGF secretion and angiopoietins in the animal model of OVC [102]. In addition, hypoxia promotes overexpression and activation of pro-angiogenic growth factors [103]. Hypoxia-inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ) targets the expression of VEGF for increasing angiogenesis [104,105]. Multiple cell lines studies reported that angiogenesis could be regulated by several inhibitors. Therefore, the application of anti-angiogenic factors can be used in the treatment purpose of cancer. In this strategy, FDA had approved the anti-angiogenic drug, bevacizumab (Avastin®) in 2004 [106]. In another way, STAT3 stabilizes HIF-1 $\alpha$  to increase the expression of VEGF, which is involved in angiogenesis [107]. The stimulated STAT3 enhances the progress of different carcinoma such as melanoma and OVC. It is essential for cell survival, proliferation, migration, invasion, and angiogenesis [108]. Park et al. [109] reported that MLT blocks angiogenesis by targeting the HIF-1 $\alpha$  under hypoxic conditions. HIF-1 $\alpha$  has been expressed in cancer cells; its degradation depends on the binding with indigenous ubiquitin ligase VHL. MLT can increase the binding of HIF-1 $\alpha$  with VHL and stimulates the degradation of HIF-1 $\alpha$  [110]. Zhang et al. [111] also reported that MLT increases binding capacity between VHL and HIF-1 $\alpha$  in glioblastoma cells.

### Effects of melatonin on the metabolism of ovarian cancer cells

Cancer cells show metabolic reprogramming to provide the energy during tumorigenesis and cancer progression [112]. Cancer cells maintain their proliferation and growth in the hypoxic and nutrient-deficient condition. In this regard, alteration of metabolism is required. Glucose and lipid are the key metabolic substrates. Cancer cells show a high rate of glycolytic activity and poor performance in the TCA cycle. Pyruvate is converted to lactate in hypoxic condition; the action is called the Warburg effect [113]. Several clinical studies revealed that serum glucose concentrations of cancer individuals are greatly raised and may be an important predictive marker for cancer. Other studies reported that more glucose transporter 1 (GLUT1) were present in OVC cells leading to enhancement of glucose uptake [114,115]. It was suggested that MLT efficiently controls the cellular metabolism at both physiological and pharmacological concentrations through different mechanisms [116]. MLT crosses cell membranes, decreases glucose uptake and lactic acid production in cancer cells [117]. Moreover, MLT inhibits insulin secretion from pancreatic  $\beta$ -cells and prevents nocturnal hypoglycemia [118]. MLT decreases protein metabolites, energy expenditure, cancer-associated proteoglycan, HIF-1 signaling, and antigen processing in OVC [3]. Additionally, MLT downregulates the expression of several enzymes or factors associated to metabolism; these include glyceraldehydes-3-phosphate dehydrogenase, pyruvate kinase isozymes (M1 and M2), aldolase A, lactate dehydrogenase A chain, creatine kinase B, protein disulfide isomerase (A3 and A6), subunit  $\alpha$  of ATP synthase, 78-kDa glucose-regulated protein and peptidyl-prolyl cis-trans isomerase A [45]. The metabolic modifications may significantly control aerobic glycolysis that leads to a decrease in proliferation and

metastasis of OVC cells. MLT also influences the overexpression of some substances like  $\beta$ -subunit of ATP synthase, fatty acid-binding protein, and 10-kD heat shock protein (HSP) in OVC cells [69].

### Melatonin therapy in ovarian cancer

Melatonin is used as a powerful integrative agent for oncotherapy, especially in ovarian cancer. Now-a-day; it is used in the combination of either radiotherapy or chemotherapy for the treatment of several cancers [46, 119]. Melatonin significantly enhances the efficacy of radiotherapy and also protects against the side effects of radiation [120,121]. Melatonin increases the tolerance power of normal tissues against the harmful effects of ionizing radiation in cancer patients who experienced radiotherapy [122]. It plays antioxidant effects with collusive roles in both chemotherapy and radiotherapy and alleviates the side effects of these treatments [46]. Cisplatin is the main chemotherapeutic drug for ovarian cancer treatment. The antioxidant properties of melatonin protect the normal tissues from large damage induced by cisplatin chemotherapy [123]. Besides these, co-treatment of both melatonin and cisplatin enhanced apoptosis in cancer cells [124]. A study reported that melatonin enhanced cis-diamine-di-chloroplatinum sensitivity in OVCAR-3 and HTOA ovarian cancer cell lines [45,125]. Melatonin co-treatment potentially boosted the apoptosis in ovarian tumor cells that leads to the progression of apoptosis/necrosis ratio and rise of the HSP70 expression [126]. Hence, melatonin induces a potent synergistic effect as an adjuvant with cisplatin therapy in ovarian cancer treatment.

### Conclusion

Ovarian cancer is a gynecological malignancy with complex molecular pathogenesis. Several molecular signals and factors such as oxidative stress, apoptosis, inflammation, alternation of metabolisms, and angiogenesis regulate its succession. It had evidenced that melatonin potentially inhibits the development and progression of this gynecological cancer through multiple ways. It had noted that chemotherapy alone is not able to decrease tumor cells, ovarian cancer cells. Therefore, new therapeutic alternatives with fewer adverse effects are extensively needed. Endogenous melatonin or its pharmacological concentrations is regarded as non-toxic. These potential roles were already established but their application has not been entirely exploited in clinical trials. The potential anti-cancer effects of melatonin along with its declining activity of adverse effects of present treatments may improve the therapeutic strategy. Thus, melatonin can be used as a suitable alternative in the treatment of ovarian cancer in the coming days.

### Conflict of interest

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