Review

Melatonin: An anticancer molecule in esophageal squamous cell carcinoma: A mechanistic review

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ABSTRACT

Several factors impact the mortality rate of patients with gastrointestinal cancers including late diagnosis, metastases to distance sites, and lack of efficacy of the conventional therapies. To reduce mortality rate, the novel effective remedies should be explored. Melatonin is an anti-inflammatory, antioxidant and oncostatic molecule and has been showed potential in controlling various malignancies. In the gastrointestinal tract, melatonin plays an important role via its membrane receptors of MT1 and MT2. It can diminish esophageal lesions resulting from acid–pepsin–bile contact and also inhibits expression of myosin light chain kinase as well as reduces its activity by regulating extracellular signal-transduction of protein kinase. The aim of the present study was to review the critical functions of melatonin in the prevention and treatment of esophageal squamous cell carcinoma including its influence on gastrointestinal pathology, oncostatic role and potential mechanisms. Particularly, the inhibitory function of melatonin on esophageal squamous cell carcinoma and its therapeutic effects are summarized. We suggest that melatonin co-treatment will enhance the efficacy of conventional treatments and survival times in patients with esophageal squamous cell carcinoma.

Key words: Melatonin, cancer, gastrointestinal tract, receptor, chemotherapy, esophageal squamous cell carcinoma

1. INTRODUCTION

Cancer is a major global health threat. Prevention of this malignancy, inhibition of cancer progression, or its entire elimination is an obvious, but to date unattainable, purpose of cancer research (1). Several factors increase the mortality rate of gastrointestinal cancer including late detection, progression to distant sites, and insufficient efficacy of the conventional therapies.

Accordingly, great effort has been made to identify more effective treatments. Since melatonin exhibits many physiological functions including anti-inflammatory, microbe inhibitory, oxidant scavenging , and oncostatic activities, it has been used to control various malignancies (2). Structurally, melatonin is an indolamine (N-acetyl-5-methoxytryptamine), with the pineal gland being the site of its circadian production (3). In addition to the pineal gland, melatonin is present in many other organs where it is also likely synthesized (4). In the gastrointestinal tract, its major activities are mediated by its membrane receptors, i.e., MT1 and MT2 while the receptor independent actions are also involved in the activities of gut and adnexa (5).

Animal studies have documented protective effect of melatonin on esophageal lesions resulting from acid–pepsin–bile contact (6). The protective mechanisms of melatonin on the esophageal cancer include inhibition both of expression of myosin light chain kinase and extracellular signal-transduction of protein kinase 1/2 (7). The purpose of the current review was to evaluate the critical function of melatonin in the prevention and treatment of gastrointestinal diseases, especially of esophageal squamous cell carcinoma.

2. MELATONIN BIOSYNTHESIS

In 1958, Lerner and his colleagues were the first to discover and purify melatonin from the bovine pineal gland (8). Thereafter melatonin has been proved to exists in other organisms including clades of invertebrates, plants and unicellular organisms such as bacteria (9-11). Melatonin is a secretory product of pineal gland by releasing into the third ventricle and the blood circulation which represents the melatonin circadian rhythm. Melatonin can also be synthesized by various tissues including bone marrow, lymphocytes, gastrointestinal (GI) tract, retina and skin (12). It has been well documented that melatonin is mainly synthesized in mitochondria (13). The precursor of melatonin is tryptophan and, then, via four enzymatic steps involved in tryptophan hydroxylase, 5-hydroxytryptophan decarboxylase, aralkylamine N-acetyltransferase and acetylserotonin-O-methyltransferase, respectively, tryptophan is converted to melatonin in vertebrates (5). During darkness, the increased secretion of noradrenaline in pineal gland activates aralkylamine N-acetyltransferase which in turn promotes melatonin production. This process mainly occurs in mitochondria, therefore, cells with a greater number of mitochondria have a high capacity for melatonin synthesis. It was estimated that the amount of melatonin produced in the digestive tract is 400 times higher than the amount produced in the pineal gland (14). Gut locally produced melatonin will protect the gastrointestinal tract from oxidative stress, inflammation and inhibit carcinogenesis (15-17).

3. FUNCTIONS OF MELATONIN IN THE GASTROINTESTINAL TRACT

The functions of GI tract are impacted by the blood melatonin rhythm. As an autocrine, paracrine, or endocrine molecule, melatonin regulates the renewal and function of the epithelium by improving the immune system of the bowel, and modulating peristalsis of gastrointestinal muscles (18). Melatonin preserves the gastrointestinal mucosa against ulcers via its antioxidant activity and enhances microcirculation and epithelial renewal (19). Studies have shown that melatonin therapy reduces the severity of NSAID-derived gastroduodenal ulcers; another noteworthy feature of melatonin in the prevention of inflammatory gastropathy (20). Melatonin also enhances the plasma levels of gastrin, luminal nitric oxide, mucosal PGE2 to exert its gastroprotective action. In addition, melatonin scavenges reactive oxygen species (ROS) due to its potent reducing activity and has anti-inflammatory actions; it represses matrix metalloproteinase-3 (MMP-3) and MMP-9 expression, which play the critical roles in the pathogenesis of gastrointestinal injury and the formation of gastric lesions (21). Moreover, melatonin strongly stimulates bicarbonate secretion from the duodenal mucosa, which

contributes to the neutralization of the stomach acid in the duodenum and also appears to stimulate acid-induced secretion (22).

Two membrane receptors are associated with melatonin's functions in mammals, i.e., MT1 and MT2. Via these receptors, melatonin represses adenyl cyclase activation and reduces intracellular cyclic AMP (cAMP) level (23). A reduced cAMP level reportedly diminishes the uptake of linoleic acid. A by-product of linoleic acid, 13-hydroxyoctadecadienoic acid, is an essential energy source for tumor signaling and proliferation; inhibition of the linoleic acid by melatonin greatly reduced tumor growth (24). The functions of melatonin are distinct in the different parts of the gut depending on whether the activated receptor is available mainly on smooth muscle cells or on enteric neurons. Transmitters produced by the enteric neurons adjust the intrinsic mechanical and electrical function of the gastrointestinal smooth muscle (25).

Melatonin also influences the expression of clock genes, as well as phosphorylation of protein kinase A (PKA) through its membrane receptor, MT1. Cholangiopathies are essential factors in the progression of hepatic failure and patient mortality (26, 27). Melatonin protects against chronic cholestatic liver damage induced by bile duct ligation (BDL) due to preserve biliary homeostasis and suppress collagen development in the hepatic tissue (28). Interestingly, the intracerebral-ventricular infusion of melatonin in rats suffering with BDL significantly reduced the biliary duct response and liver tissue fibrosis by suppressing expressions of GnRH and its receptor (29). Increasing darkness exposure of BDL rats to prolong their nocturnal melatonin rise also enhances melatonin levels in the cholangiocyties and reduces fibrosis progression. It is suggested that the elevated pineal melatonin production may also prevents the progression of other cholestatic liver disorders. On the other hand, melatonin's inhibition on hypothalamic GnRH production with its local action substantially enhances its protective effect against cholangiocyte-related disorders since GnRH promotes biliary destruction and fibrosis development by directly acting on the cholangiocyties. Thus, melatonin alone or as a co-treatment may have potent capacity in protecting against variety of hepatic disorders (26).

4. ONCOSTATIC ACTIVITY OF MELATONIN: PROPOSED MECHANISMS

The expression miR-424-5p is upregulated by melatonin. miR-424-5p targets VEGFA 3'UTR and suppresses its expression. As a result, melatonin inhibits tumor angiogenesis in osteosarcoma (30). The miR-152-3p expression is also enhanced by melatonin while its targeted gene expressions (IGF-IR, HIF-1α and VEGF) are reduced (31). Under hypoxia conditions, melatonin at pharmacological concentrations, inhibited VEGF mRNA and protein levels via reduction of (HIF)-1a protein levels (32). It has also been reported that melatonin inhibits HIF-1a leading to downregulation of VEGF expression in the HCT116 human colon cancer cell line (33) also in a mouse tumor model (34). Jardim-Perassi *et al*. have reported that tumor size, cell proliferation (ki-67), expression of VEGF receptor 2 and Von Willebrand Factor were all suppressed by melatonin in mice (35). Elsewhere, melatonin downregulates endothelin-1 mRNA which is a survival factor of colon cancer cells via inactivation of FoxO1 and NF-kB transcription factors. Melatonin enhances the phosphorylation of Src to active PKA which in turn promotes phosphorylation and inactivation of FoxO1. Moreover, melatonin increases the dephosphorylation of Akt and ERK and diminishes PKC activity leading to the inactivation of the NF-kB transcription factor (36). The expression of Rho-associated kinase1 protein is downregulated in MDA-MB-231 metastatic cell lines due to the synergic effects of melatonin and Y27632 and this combination also decreases viability and invasion/migration in both MDAMB-231 and MCF-7 breast cancer cell lines (37). Melatonin transcriptionally downregulates MMP-9 through a reduction of p52- and p65-DNA-binding activity and regulates cell motility and MMP-9 transactivation by the Akt-mediated JNK1/2 and ERK1/2

signaling pathways. These results reveal melatonin's regulatory actions on metastasis of cancer cells (38).

Metabolically, melatonin suppresses the aerobic glycolysis and linoleic acid uptake in tumor cells and lowers the release of 13-hydroxyoctadecadienoic acid, cAMP levels and DNA content. Melatonin also suppresses the phospho-activation of ERK 1/2, AKT, GSK3b and NF-kB. All these actions of melatonin render its suppression on tumor growth and invasion in isolated human leiomyosarcoma (39). Melatonin downregulates MDM2 (E3 ubiquitin ligase) gene expression which promotes upregulation and acetylation of P53 leading to cell cycle arrest via elevated p21 levels. Melatonin also reduces sirt1 to inhibit p300 activity and enhances MDMX and p300 levels. Consequently, melatonin induces apoptosis and growth inhibition of tumor cells (40). Pharmacological concentrations of melatonin have pro-apoptotic and anti-proliferative effects on colorectal cancer LoVo cells through the nuclear import of histone deacetylase 4 which is required for preventing of H3 acetylation of the bcl-2 promoter and suppressing its expression. The nuclear import of histone deacetylase 4 is mediated by Ca2+/calmodulin-dependent protein kinase II alpha inactivation (41). Leja-Szpak *et al*. have reported that melatonin provokes pro-apoptotic factors such as Bcl-2/Bax and caspase-9 proteins mediated by MT1/MT2 in pancreatic carcinoma cells (42). Melatonin also downregulates SOX9 expression to reduce the self-renew of stem cells and leads to an inhibition of osteosarcoma stem cells and metastasis (43). In many cancers, ROS enhances AKT phosphorylation leading to an elevation of cyclin D1, PCNA, and Bcl-2 expression and downregulation of Bax.

Melatonin inactivates Akt in the *in vitro* and *in vivo* conditions and abolishes proliferation and apoptosis resistance of tumor cells and also lowers the levels of Snail and Vimentin and enhances E-cadherin. Moreover, ROS-activated extracellular-regulated protein kinase (ERK) and PI3K/Akt pathways contribute to the enhancement of HIF-1α and VEGF during malignancy; however, melatonin scavenges ROS and inactivates these factors. Based on these evidents, melatonin may play roles in suppressing tumor cell survival, metastasis and angiogenesis (44) (Figure 1). Melatonin increases miR-34a/449a cluster expression which targets Bcl-2 and Notch1 mRNA and this results in decreased colorectal cancer cell proliferation, viability and elevated apoptotic (45). Melatonin reduces lung cancer stemness and cell marker and the signaling pathways including PLC, ERK/P38, B-catenin, Twist which contributes to the inhibition of CD133 function and lung cancer stemness by melatonin (46). In nasopharyngeal carcinoma cells, melatonin improves cisplatin antitumor activity through inhibition of both the nuclear translocation of B-catenin and also the reduction of response of Wnt/B catenin. In addition, melatonin can overcome cisplatin chemoresistance in NPC cells (47-49).

An earlier study has reported that melatonin enhances the function of apoptotic and autophagy-related proteins which are incapacitated via endoplasmic reticulum (ER) stress and autophagy inhibitors. Furthermore, melatonin suppresses the gastric cancer cell expansion through activation of the IRE/JNK/Beclin 1 signaling pathway (50). These findings indicate that melatonin suppresses ER stress pathway. Melatonin treatment reduces HT-29 cell viability and the observation has been confirmed in SW48 and Caco-2, respectively. These data suggest that melatonin causes autophagy through ER stress genes in colorectal cancer cells (51). The anti-ER stress activity of melatonin has also observed in hepatocytes which are subjected to H_2O_2 by modifying HSP90 and HSP70 levels. This modifies NF-κB nuclear translocation, ERK/AKT/cytosolic function of the signal transduction pathways. In addition, melatonin treatment modulates the MAPK pathway, which relates to the reduction of ERK1/2 and AKT function to the basal level (52, 53). Chuffa *et al*. have shown that functions of several proteins are essential in TLR4-mediated signaling pathway in ovarian cancer during ethanol intake. These proteins include TLR4, MyD88, NF-κB, inhibitor of NF-kB alpha, IKb kinase alpha,

TNF receptor-associated factor 6, TRIF, interferon regulatory factor 3, interferon β, tumor necrosis factor alpha, and interleukin (IL)-6. In ovarian cancer tissue, melatonin reduces IFN-β, TNF-α, and IL-6. MyD88- and TRIF-dependent signaling pathways are significantly downregulated by melatonin due to the decreased inflammatory response in ethanol-preferring rats with ovarian cancer. These findings indicate that melatonin suppresses the inflammatory factors (IkBα, NFkB p65, TRIF and IRF-3) during ethanol consumption (54). Melatonin causes ovarian cancer cell apoptosis with the overexpression of the BAX, P53, cleaved caspase-3 (55), cleaved caspase-9 and downregulation of CDC25A, phospho-CDC25A (at Ser75), phospho-21 (at Thr145). Moreover, melatonin-mediated apoptosis in cancer cell involves in mitochondrial function. Melatonin not only directly upregulates P53 but also downregulates its upstream regulators including MDM2, phospho-MDM2 (at Ser166) and AKT, phospho-AKT (at Thr308). Suppression of the AKT/MDM2 intracellular pathway by melatonin is observed in SGC-7901 gastric cancer cells (56). Melatonin inhibits COX-2, prostaglandin E2, P300, NFkB signaling while its suppression on PI3K/Akt signaling pathway is mediated by inhibition of phosphorylation of PI3K, Akt, PRAS40, GSK-3 proteins. Remarkably, activation of the Apaf-1 apoptosis pathway by melatonin is mediated by cytochrome C release, cleaved caspase-3, caspase-9 in breast cancer cells (57). The oncostatic actions of melatonin are illustrated in Figure 1 and summarized in table 1.

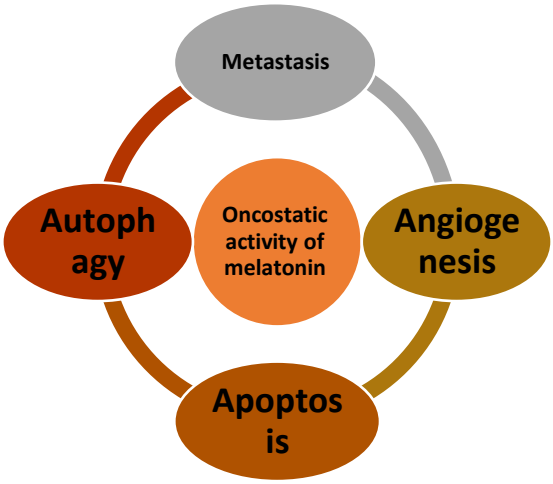

Fig 1. The potential associations of melatonin's oncostatic activities with autophagy, apoptosis, angiogenesis and metastasis.

Table 1. Summarization of the oncostatic mechanisms of melatonin on cancer cells

Studies	Mechanisms
Vimalraj *et al* . (30)	Melatonin upregulated the expression miR-424-5p which targeted VEGFA 3'UTR and inhibited tumor angiogenesis.
Marques *et al*. (31)	Melatonin enhanced miR-152-3p expression which targeted genes expression (IGF-IR, HIF-1α and VEGF).
Dai *et al*. (32)	Under hypoxia condition, melatonin at pharmacological doses inhibited VEGF mRNA and protein levels via reduction of (HIF)-1a protein levels.
Park *et al*. (33)	Melatonin inhibited HIF-1a leading to downregulation of VEGF expression.
Kim *et al*. (34)	Melatonin exerted anti-angiogenic effects by targeting HIF-1a.
Jardim-Perassi *et al.* (35)	Tumor size, cell proliferation (ki-67), expression of VEGF receptor 2, Von Willebrand Factor were reduced in mice treated with melatonin
León *et al*. (36)	Melatonin decreased endothelin-1 mRNA via inactivation of FoxO1 and NF-kb transcription factors.

Borin *et al*. (37)	The expression of Rho-associated kinase1 protein was downregulated in MDA-MB-231 metastatic cell lines with co-treatment of melatonin and Y27632.
Lin *et al*. (38)	Melatonin downregulated MMP-9 through a reduction of p52- and p65-DNA-binding activities and regulated cell motility and MMP-9 transactivation by the Akt-mediated JNK1/2 and ERK1/2 signaling pathways.
Mao *et al.* (39)	Melatonin inhibited the aerobic glycolysis and tumor linoleic acid uptake, release of 13-hydroxyoctadecadienoic acid, tumor cAMP level and DNA content. It suppressed the phospho-activation of ERK 1/2, AKT, GSK3b and NF-kB.
Proietti *et al*. (40)	Melatonin reduced MDM2 expression, upregulated P53 and p21. Also, it reduced sir1 and enhanced MDMX and p300 levels.
Wei *et al*. (41)	Melatonin had pro-apoptotic and anti-proliferative effects through the nuclear import of histone deacetylase 4 which mediated by Ca2+/calmodulin-dependent protein kinase II alpha inactivation.
Leja-Szpak *et al*. (42)	Melatonin provoked Bcl-2/Bax and caspase-9 proteins by interaction with the Mel-1 A/B receptors.
Qu *et al*. (43)	Melatonin downregulated SOX9 expression which increased the self-renew of stem cells.
Liu *et al*. (44)	Melatonin inactivated Akt leading to reduction of cyclin D1, PCNA, Bcl-2, Snail,Vimentin, HIF-1α and VEGF as well as to enhancement of the expression of Bax and E-cadherin.
Ji *et al*. (45)	Melatonin increased miR-34a/449a cluster expression which targeted Bcl-2 and Notch1 mRNA.
Yang *et al*. (46)	Melatonin was able to suppress PLC, ERK/P38, B-catenin, Twist signaling pathway which is contributed to CD133 function and lung cancer stemness.
Zhang *et al.* (47)	Melatonin enhanced Cisplatin antitumor activity through inhibition of both the nuclear translocation of B-catenin and also the reduction of response function of Wnt/B catenin.
Zheng *et a*l. (50)	Melatonin suppressed the advancement of gastric cancer cell expansion through activation of the IRE/ JNK/ Beclin 1 signaling pathway.
Chok *et al*. (51)	Melatonin caused autophagy through endoplasmic reticulum stress genes in colorectal cancer cells.
Moniruzzaman *et al.* (52)	Melatonin modified NFKB nuclear, ERK/AKT/Cytosolic function, MAPK signaling pathways and HSP90 and HSP70.
Chuffa *et al.* (54)	MyD88- and TRIF-dependent signaling pathways were incapacitated via melatonin.
Chuffa *et al*. (55)	Melatonin promoted apoptosis and over expression of the BAX, P53, and Cleaved caspase-3.
Song *et al*. (56)	Melatonin suppressed AKT/MDM2 intracellular pathway.
Wang *et al.* (57)	Melatonin inhibited COX-2, prostaglandin E2, P300, NFkB signaling, inactivated PI3K/Akt signaling pathway, activated the Apaf-1 apoptosis pathway.

5. MELATONIN'S ROLES IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Melatonin is an important immune regulatory molecule and an potent antioxidant (58). It protects DNA from oxidative damage, scavenges free radicals, promotes antioxidant enzymes and activates DNA repair mechanisms (59). In addition, it modulates the release of cytokines, increases immune cell viability and improves cell metabolism (60). It stimulates T cell and natural killer (NK) activities (61). Numerous studies have also reported antiproliferative, antimigratory and proapoptotic functions of melatonin involving a variety of different signaling pathways in tumors (62-65). In cancer cells, melatonin increases the expression of BAX/BAK, Apaf-1, caspases and p53 and inhibits Bcl-2, AKT/MDM2 intracellular pathway (56, 65, 66).

The anti-angiogenic effect of melatonin in growing tumors has often been observed. In breast cancer cells, melatonin downregulates miR-148a-3p, IG-IR and VEGF (67). Moreover, melatonin also inhibits HIF-1 and STAT3 signaling pathway in HepG2 liver cancer cells (68). Melatonin also interferes with metastases via modulation of cell–cell and cell–matrix interaction, extracellular matrix remodeling by matrix metalloproteinases, cytoskeleton reorganization, reducing the epithelial–mesenchymal transition, and angiogenesis (4). The anti-inflammatory activities of melatonin are well documented. It reduces inflammatory mediators such as IL-6, IL-8, COX-2, and NO. Additionally, it suppresses the expression of NF-kB and DNA demethylation. As a result, melatonin has a major function in preventing the disfigurement of DNA (69).

Metabolically, melatonin inhibits glycolysis, the tricarboxylic acid cycle, and pentose phosphate pathway in prostate cancer, therefore suppresses the growth of tumors (70).

In esophageal squamous cell carcinoma, melatonin increases sensitivity of ESCC cells to 5-fluorouracil via the inhibition of the Erk and Akt pathways. The expression levels of pMEK, pErk, pGSK3β and pAkt are suppressed in cells treated with melatonin. This indolamine exhibits antiproliferation, antimigration, proapoptotic effects and suppresses tumor growth both *in vitro* and *in vivo* (71). Tan *et al*. have reported that melatonin suppresses ERK-mediated activation of MLCK. Accordingly, melatonin exerts protective effects on the esophageal epithelial barrier (72). A recent study has shown that melatonin inhibits esophageal cancer cells metastasis by suppressing NF-κB signaling pathway, downregulating MMP9 along with a high level of E-cadherin (73). Melatonin increases esophageal mucosal blood flow (EBF) and PGE2 level, reduces TNFα content, activates COX-PG and NOS-NO systems and stimulates capsaicin-sensitive afferent nerve endings to promote recovery of esophageal injury (74).

Gastroesophageal reflux disease (GERD) is a chronic digestive condition that is a risk factor for esophageal carcinoma (75). A recent study has shown that melatonin suppresses GERD. The GERD patients treated with melatonin have significant increase in serum gastrin, pH and a significant reduction in basal acid output, and an improvement in heartburn and epigastric pain (7). Patients with GERD treated with a dietary supplementation containing melatonin, l-tryptophan, vitamin B6, folic acid, vitamin B12, methionine and betaine significantly reduces their symptoms faster than those treated with 20 mg omeprazole (76). Melatonin also reduced esophageal injury induced by acid–pepsin and acid–pepsin–bile exposure in animal model (6). In addition, melatonin inhibits phase G0/G1 of cell cycle and the tumor growth in cell line Eca-109 (77). A case report showed that a male patient (age, 70) with esophageal carcinoma when he was treated with somatostatin, melatonin, retinoids, vitamins C, D3 and E, calcium, sulfated aminoglycosides and minimum doses of cyclophosphamide, his quality of life is improved (78).

6. THERAPEUTIC EFFECTS OF MELATONIN IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

The use of melatonin for the management of gastrointestinal cancer has received great attention as a potential alternative therapy; this relates to its high safety profile, its anti-cancer actions, and finally its very low toxicity (79). Melatonin co-administration with other therapeutic agents enhances their efficacy (80). GERD, Barrett's esophagus, and obesity are important risk factors in the initiation of esophageal adenocarcinoma (81, 82). Studies have reported that in patients with GERD and repetitive duodenal lesions, melatonin levels are lower than that in healthy individuals. Melatonin supplementation prevents peptic modification caused by the esophageal and duodenal mucosa injury (7, 83). Melatonin is effective in preserving the esophageal mucosa intact via increasing its blood flow and anti-inflammatory capacity; this is apparent in GERD patients and those suffering with extensive esophageal

damage (74). It has also been suggested that the esophago-protective action of melatonin against GERD may associate with the repressive action of this indolamine on gastric acid release, melatonin induces gastrin secretion, which reduces the gastro-esophageal reflux by increasing contraction of the lower esophageal sphincter (84). Melatonin can elevate luminal levels, gastric blood flow and mucosal PGE2 generation further strengthening its gastroprotective effect (21). Free radical associated oxidative stress is an important risk factor to damage the esophageal and gastric mucosa. Melatonin, in addition to being a potent direct radical scavenger, also stimulates a number of antioxidative enzymes including glutathione peroxidase/reductase and glucose- 6-phosphate dehydrogenase while repressing pro-oxidative enzymes, therefore, it can prevent esophageal and gastric mucosa damage from oxidative stress. Melatonin significantly represses the expression of Akt and Erk signaling which play key roles in esophageal cancer and also efficiently reduces 5-Fu cytotoxicity in esophageal squamous cells (71). Moreover, melatonin reduces VEGF level in patients with progressive cancer (33). The co-administration of melatonin with common anticancer medications helps to amplify the therapeutic efficiency. Data has shown that oncostatic activity of melatonin is not tissue-specific and exhibits protective effect against cancers derived from different cell types and tissues. In summary, because of its wide spectrum of anti-tumor effects, its high efficacy in cancer inhibition and its low side effects, melatonin deserves more clinical trials not only in esophageal cancer but in other cancer types too.

7. CONCLUSION

Many studies have documented the beneficial effects of melatonin in GI disorders. In addition, its potential use as a cancer suppressor has drawn great attention currently. The mechanisms are related to its antioxidant, anti-inflammatory, and oncostatic properties. Particularly, its antitumor effects are also related to its anti-angiogenic, immune regulatory, proapoptotic and antimetastatic functions. Thus, melatonin alone or in combination with other chemotherapeutical medicines may be a worthwhile option to be considered for various GI diseases including cancers.

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AUTHORSHIP

SMM designed the idea for the article. AAJ performed the literature search. NH, MYM and SR wrote the first draft of the manuscript. RJR and ZAB reviewed and revised the manuscript. SMM reviewed and approved the final version of the manuscript.

CONFLICT INTEREST

The authors declare no conflicts of interest.

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