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REVIEW

Therapeutic applications of melatonin in disorders related to the gastrointestinal tract and control of appetite

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Abstract

Most animals have large amounts of the special substance melatonin, which is controlled by the light/dark cycle in the suprachiasmatic nucleus. According to what is now understood, the gastrointestinal tract (GIT) and other areas of the body are sites of melatonin production. According to recent studies, the GIT and adjacent organs depend critically on a massive amount of melatonin. Not unexpectedly, melatonin's many biological properties, such as its antioxidant, anti-inflammatory, pro-apoptotic, anti-proliferative, anti-metastasis, and antiangiogenic properties, have drawn the attention of researchers more and more. Because melatonin is an antioxidant, it produces a lot of secretions in the GIT's mucus and saliva, which shields cells from damage and promotes the development of certain GIT-related disorders. Melatonin's ability to alter cellular behavior in the GIT and other associated organs, such as the liver and pancreas, is another way that it functions. This behavior alters the secretory and metabolic activities of these cells. In this review, we attempted to shed fresh light on the many roles that melatonin plays in the various regions of the gastrointestinal tract by focusing on its activities for the first time.

Keywords Melatonin · Gastrointestinal tract · Antioxidant · IBD

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Introduction

Melatonin, also known as N-acetyl-5-methoxy tryptamine, is a hormone that is produced by the pineal gland and other tissues such as the skin, retina, gut, brain, lens, and bone marrow. Melatonin is essential for many physiological processes including immune modulation, sleep promotion, and anti-inflammatory and anticancer effects (Roohbakhsh et al. 2018). As an antioxidant agent, melatonin possesses anti-inflammatory and anti-excitatory effects by scavenging hazardous free radicals formed in the body (Zisapel 2018). Oncostatic properties, immune regulation, sleep promotion, involvement in mood disorders, controlling of puberty timing, regulation of reproduction, and transplantation are other important functions of melatonin (Ahmad et al. 2023). So, any dysfunction in melatonin synthesis or production has been demonstrated to be correlated with the initiation of a broad range of human disorders including neurodegenerative disorders, circadian rhythm-related sleep disorders, and cancers. Due to its potential analgesic effects, melatonin is also applied in pain-associated diseases (Morin 1999). As mentioned, it should be noted that melatonin is also synthesized by the enterochromaffin cell of the gastrointestinal tract

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(GIT). In this organ, melatonin is released into the bloodstream in reaction to meal consumption. Consequently, the GIT has more melatonin than the pineal gland and blood circulation due to the size of the digestive system (Sjöblom et al. 2001). Consequently, melatonin can be quite essential in the GIT due to its high concentration of the hormone per gram of tissue (Bubenik 2002). Thus, in this review, we will concentrate on the several roles that melatonin plays in the GIT. We start our investigation of melatonin's function in the oral cavity by highlighting both its protective and anti-inflammatory properties. Subsequently, we want to explore the many activities of melatonin in the stomach, followed by its processes in the intestine and its participation in a variety of gut-related diseases. Lastly, we will review the significance of melatonin in hunger and provide an outline of how it functions in the pancreas and liver, two significant organs connected to the gastrointestinal tract.

Melatonin mechanism of action in the oral cavity

In the oral cavity, high exposure to reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to inflammatory diseases (Cutando et al. 2007). In this line, defense mechanisms produce ROS and RNS to reduce pathogenic microorganisms. So, the imbalance between oxidants and antioxidants has been recognized as a risk factor for chronic oral inflammatory diseases (Bagan et al. 2014; Yang et al. 2019; Zhang et al. 2023). Melatonin acts as an anti-inflammatory agent in bone remodeling, osseointegration of dental implants, periodontal disease, and oral cancer (Tachibana et al. 2014). By passive diffusion, melatonin enters the oral cavity in the saliva, which contains high concentrations of melatonin (Çevik-Aras and Ekström 2010). Salivary melatonin represents the percentage of circulating melatonin that is not albumin-bound (Arias-Santiago et al. 2012). Melatonin and its metabolites are important antioxidants that reduce oxidative stress in fibroblast cells (Phiphatwatcharaded et al. 2017). Also, melatonin has a capacity for chelating metals like iron (III), copper, and zinc, which causes a decrease in their cytoplasmic availability (Gulcin et al. 2003). In addition, melatonin is implicated in the section of chloride and bicarbonate ions, sodium, and potassium in salivary ducts (Arias-Santiago et al. 2012). It is also known that melatonin neutralizes the increased production of inflammatory mediators like tumor necrosis factor-α (TNF-α) and several interleukins and decreases neutrophil infiltration (Fig. 1) (Cobo-Vázquez et al. 2014; Khomari et al. 2021).

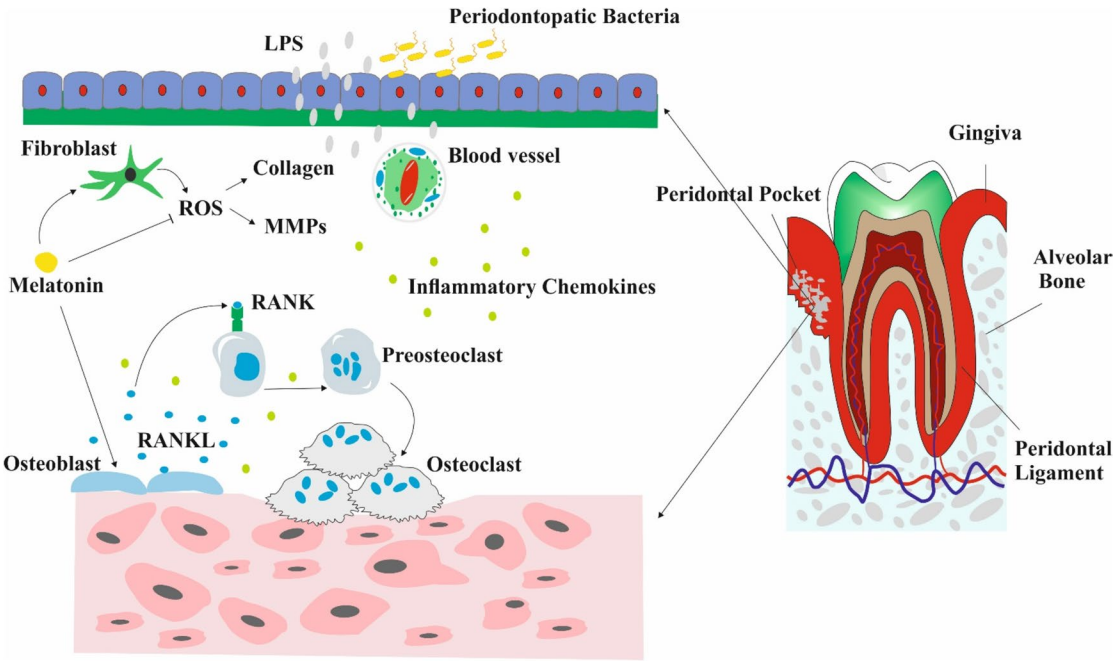

Fig. 1 Tissue deterioration is caused by inflammatory mediators such as MMPs and ROS, which influence collagen breakdown. Melatonin treatment of human gingival fibroblasts increases the levels of collagen III a1 mRNA while decreasing the expression of MMP1. In addition, melatonin inhibits osteoclast activity and increases osteoblast activity, protecting periodontal tissues from inflammatory mediators. Through contact with its receptor RANK, which is expressed on the surface of osteoclasts, RANKL, a protein produced by osteoblasts, plays a crucial role in the creation and function of osteoclasts. RANKL concentrations in saliva are decreased by melatonin. RANKL: receptor activator of the NF-kB ligand. MMPs: matrix metalloproteinase. LPS**:** lipopolysaccharide

Role of melatonin in the inflammatory condition of the oral cavity

A chronic inflammatory immune-mediated disease of the oral mucosa, oral lichen planus (OLP), is linked to a higher risk of mouth cancer and is considered to be possibly malignant (Agha-Hosseini et al. 2012). The clinical characteristics of OLP consist of Wickham striae, some redness, and white lines on the oral mucosa (Lavanya et al. 2011). In the early phase of OLP, the production of inflammatory mediators occurs through an inflammatory response in oral mucosal tissue. The signaling molecules, such as TNF-α and NF-kB, repress the synthesis of pineal melatonin, leading to the migration of immune cells from the bloodstream into the connective tissue of oral mucosa (Nabi-Afjadi et al. 2023a; Sharbatdar et al. 2023; Zhou et al. 2009). In the chronic phase of OLP, oral immune response dysregulation improves the accumulation of free radicals and oxidative stress molecules, which lead to oral mucosal damage. Furthermore, oral epithelial cell permeability is influenced by changes in the biosynthesis of melatonin and its receptors through chronic inflammation in the oral mucosa (Chaiyarit et al. 2017; Thongprasom et al. 2006). Melatonin and melatonin 1 receptor (MT1) are increased in the oral mucosa of OLP patients in contrast to the control (Chaiyarit et al. 2017). After radiotherapy, oxidative stress markers, such as malondialdehyde (MDA), total oxidant status (TOS), and oxidative stress index (OSI), were reduced by melatonin, and catalase and glutathione levels were enhanced. So, in other words, melatonin decreases the salivary gland damage generated by irradiation (Cakmak Karaer et al. 2016).

Moreover, melatonin inhibits cancer cell growth by modulating DNA methylation and histone acetylation pathways (Niles et al. 2013; Sharma et al. 2008; Zhang et al. 2023). According to Yang et al. findings, histone lysine-specific demethylase (LSD1) was overexpressed in oral cancer tissues of clinical patients and patient-derived tumor xenograft (PDTX). Melatonin downregulated LSD1 expression, decreased its mRNA levels, and provoked H3K4 and H3K9 acetylation. Melatonin also caused cell cycle arrest in the G0/G1 phase. These data suggest that melatonin is a possible therapeutic option for LSD1-overexpressing oral cancer (Yang et al. 2017a).

On the other hand, it is well known that the breakdown of the basement membrane is a significant step for metastasis and invasion, which needs the activation of proteolytic enzymes, such as matrix metalloproteinases (MMPs). MMP-9 is an important target of melatonin for the regulation of cancer metastasis (Shah et al. 2009). In a study performed by Yeh et al., 12-O-tetradecanoyl phorbol-13-acetate (TPA) was used to induce the MMP-9 expression. This study revealed that melatonin, through ERK1/2 phosphorylation, repressed the TPA-induced MMP-9 expression of oral cancer cells. They also demonstrated that melatonin inhibited the expression of a CREB-binding protein (CREBBP) and E1A-binding protein p300 (EP300) transcription factors and decreased histone acetylation on the MMP-9 gene (Yeh et al. 2016). More recently, a study performed by Liu et al. also established that melatonin upregulated E-cadherin levels and downregulated the expression of p-Akt, Snail, and Vimentin. Also, their result indicated that melatonin suppresses oral cancer metastasis by decreasing ROS-dependent Akt activation (Liu et al. 2018a, b).

Protection action of melatonin against gingivitis and periodontitis

The periodontium is made of soft (periodontal ligament and gingiva) and hard (cementum and bone) tissue, which control teeth function (Bartold and Narayanan 2006). Microorganisms in the periodontium can cause pathological alterations that result in the production of harmful chemicals such as lipopolysaccharide (LPS), which can cause an inflammatory reaction (dos Santos et al. 2018).

Inflammatory mediators including ROS, IL6, and MMPs are released when periodontal disease occurs, affecting collagen breakdown and ultimately resulting in tissue loss. Meanwhile, fibrosis and scarring are the outcome of inadequate tissue repair (Bartold and Narayanan 2006; Lin et al. 2015). In periodontitis patients, melatonin levels are low in saliva and gingival crevicular fluid compared to the healthy control. So, salivary melatonin level is possibly a sign of periodontal disease severity (Cutando et al. 2006). In 2019, Bertl et al. demonstrated that salivary melatonin levels were lower in periodontitis patients before therapy compared to healthy controls and notably associated with clinical periodontal parameters. After periodontal therapy, salivary melatonin levels were significantly enhanced and negatively related to a decrease in local inflammation (Bertl et al. 2013). Accumulating evidence indicates that the treatment of human gingival fibroblast (HGF) with melatonin also enhances collagen III a1 (COL3A1), Decorin (DCN), tissue inhibitor of metalloproteinase1 (TIMP1), and IL10 mRNA levels while downregulating MMP1 expression. In addition, melatonin treatment reduces the MMP1/TIMP1 protein ratio, leading to a decrease in MMP-related ECM destruction. So, regulation of the MMPs through melatonin is a potential therapeutic strategy to reduce the progression of periodontal disease (Gómez-Florit et al. 2013).

On the other hand, melatonin attenuates the expression of inflammatory mediators by suppressing NF-κB activation. According to Hosokawa et al., melatonin reduced IL-1β-induced CXC chemokine ligand (CXCL) 10 and MMP-1 production and improved TIMP-1 production in human periodontal ligament cells (HPDLC). In addition, they reported that p38 MAPK, JNK phosphorylation, and IkB-α degradation were

repressed by melatonin in IL-1β-stimulated HPDLC. These results indicate that by controlling MMP and TIMP production in periodontal lesions, melatonin inhibits the initiation and progression of periodontal disease (Hosokawa et al. 2016).

Melatonin promotes the gingival index and pocket depth while diminishing salivary concentrations of receptor activators of the NF-κB ligand (RANKL) and salivary concentrations of osteoprotegerin (OPG). Cutando et al. suggest that melatonin influences osteoclastogenesis, enhances the property of alveolar bone, and inhibits the progression of periodontal disease (Cutando et al. 2014). Melatonin also exerts its influence through Mel1aR on tooth development. Tooth development is under the regulation of systemic hormones in the same way as skeletal growth. Via physiological regulation of odontogenic cells, melatonin mediates the growth of the tooth and surrounding jaw bone. At the late stage of tooth development, Mel1aR is expressed in some kind of odontogenic cells in the tooth germs. Melatonin shows positive influences on the proliferation and odontoblastic differentiation of human dental papilla cells (Kumasaka et al. 2010; Tachibana et al. 2014).

Melatonin and stomach secretion

The protective role of melatonin on gastric mucosa is due to the inhibition of gastric acid and pepsin secretion. Gastric acid and pepsin are two important invasive factors in the pathogenesis of gastric ulcers and are associated with stress-induced gastric mucosal injuries (Kato et al. 1998). It has been observed that in animal models of chronic gastric fistula, melatonin reduced gastric acid and also increased plasma gastrin levels (Konturek et al. 1997). In addition, intracisternal injection of melatonin in rat's pylorus-ligated consciousness reduced secretion of gastric acid and pepsin in a dose-dependent manner. It is suggested that this inhibitory effect of melatonin is related to the central nervous system (CNS) (Kato et al. 1998). Luminal melatonin is a powerful stimulant for HCO^{-}_{3} secretion by the duodenal mucosa. It is also believed that melatonin controls the secretion of alkaline in the presence of acid in the lumen (Sjöblom and Flemström 2003). Melatonin has been shown to protect the gastrointestinal mucosa by stimulating the production of mucosal HCO-3 by causing the release of intracellular Ca+2 in the enterochromaffin cells through the MT2 receptor (Ataee et al. 2017; Bubenik 2002).

Melatonin and mucosal protection and ulcer healing

Stomach ulcers are mainly present at the antral site, followed by gastric mucosal injuries (Bandyopadhyay et al. 2001). By speeding up the oxidation process, aspirin, a nonsteroidal anti-inflammatory medicine, stimulates the generation of hydrogen peroxide (H2O2), which in turn creates deadly hydrochloric acid (via Cl- and H2O2). This finally causes gastrointestinal damage such as ulcers and upper gastrointestinal hemorrhage as well as mucosal peroxidation (Moharram et al. 2017). The clinical symptoms of gastric ulcers include common epigastric pain and, in severe cases, observation of blood in the vomitus. These ulcers are also referred to as peptic ulcers, as the production of pepsin and hydrochloric acid typically exacerbates them (Bandyopadhyay et al. 2001). These lesions involve 5 to 10% of the world's people throughout their lives. Gastric acid, cytokines, interleukin-1, and TNF-α have a key role in inducing mucosal damage (Moharram et al. 2017). Gastrointestinal ulcers are created when the balance between toxic and defensive factors is disrupted. The endogenous destructive factors include hydrochloric acid, pepsin, refluxed bile, leukotrienes, and ROS such as the superoxide anion ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($^{\bullet}OH$) and external destructive factors including alcohol, steroidal and nonsteroidal anti-inflammatory drugs, stress, and *Helicobacter pylori*. The gastric mucosa, through the mucus-bicarbonate barrier, prostaglandin, mucosal blood flow, migration of cells and antioxidants, and anti-oxidative enzymes, can play a protective and defensive role against these invasive factors. It has been proven that ROS plays a key role in the pathogenesis of gastric ulcers in studies that focused on ischemia-reoxygenation-induced gastric mucosal injury (Bandyopadhyay et al. 2001). ROS is one of the most important factors in the pathogenesis of gastric mucosal lesions that increases lipid oxidation, which subsequently damages the cell membranes and intercellular molecules. In this context, the inhibitory role of melatonin in preventing and healing stomach ulcers is discussed (Bandyopadhyay et al. 2001). It has been proven that melatonin amount in the digestive system is 400 times greater than the pineal gland (Konturek et al. 2010; Konturek et al. 2006; Sjöblom and Flemström 2003; Taslidere et al. 2018). Also, a high level of melatonin has been found in the bile, and melatonin-binding sites have been observed in the stomach, jejunum, ileum, and colon (Bandyopadhyay et al. 2001). The synthesis of melatonin in the GIT is not associated with the production of the pineal gland, but in GIT, the synthesis of melatonin occurs during the day and alternately after the meal. The regulation of melatonin in the peripheral blood is regulated by melatonin from GIT origin and is also influenced by a high concentration of tryptophan (precursor of melatonin) (de Talamoni et al. 2017). Because they contain the essential melatonin synthesis enzyme, hydroxy-indole-O-methyltransferase (HIOMT), the enterochromaffin-like cells of the GIT are the primary source of melatonin in the organ (Brzozowska et al. 2002; de Talamoni et al. 2017). As mentioned above, melatonin has received special attention in the past

10 years for its ability to scavenge free radicals and act as an antioxidant. Furthermore, it has been demonstrated in gastric ulcer models that melatonin shields the stomach mucosa from oxidative damage brought on by reactive oxygen species (Bandyopadhyay et al. 2001; Brzozowska et al. 2002; Konturek et al. 2006). It has been reported that melatonin in ulceration healing inhibited the secretion of HCl and pepsin and also eliminated intracellular ROS. In addition, melatonin has been shown to reduce the gastric ulcer rate and the level of tissue MDA and increase superoxide dismutase (SOD) activity and glutathione (GSH) levels in inducible conditions for stomach ulceration such as ischemia, ethanol, and acetylsalicylic acid (ASA) (Noorbakhsh Varnosfaderani et al. 2023; Taslidere et al. 2018). Abdelraheim et al. suggested that the healing of gastric ulcers by melatonin is associated with ghrelin biosynthesis and GSH and reducing MDA content (de Talamoni et al. 2017). Additionally, melatonin prevents ethanol, ischemia, stress, and aspirin-induced stomach ulcers by preventing inflammation caused by the accumulation of polymorphic neutrophils, preventing the loss of GSH levels, and increasing stomach prostaglandin levels. Most effects of melatonin in the GIT are related to the membrane and nuclear receptors, although some of its other functions are independent of these receptors. There are three membrane receptors in which the MT1 and MT2 have a high homology in amino acid content and are expressed throughout the GIT, especially in the enterochromaffin cells (MT2 is predominantly expressed). These two receptors are G-protein-coupled, and when they are activated, a range of intracellular messengers such as cAMP, cGMP, or Ca^{+2} are modulated (de Talamoni et al. 2017; Konturek et al. 2010). Some evidence has also shown that the mechanism of melatonin in healing gastrointestinal damage is due to the activation of cyclooxygenase (COX), prostaglandin (PG) system, and nitric oxide synthase (NOS) systems. One of the symptoms of gastric ulcer healing by melatonin is an increase in hyperemia at the margin of the ulcers, either due to the presence of melatonin or because of the presence of potent vasodilators such as NO or PGE_2, with the origin of vascular endothelium, gastric epithelium, and capsaicin-sensitive nerve endings. In this way, suppressing COX by a nonselective inhibitor, such as indomethacin, reduces the protective effect of melatonin and L-tryptophan against mucosal ulceration. It has been demonstrated that nitric oxide (NO) plays a crucial role in the way that melatonin functions to heal gastric ulcers. When L-NNA is added as an NOS inhibitor, the release of NO from the luminal is inhibited, which lowers the mucosal hyperemia that is caused by melatonin or L-tryptophan at the ulcer margin (Konturek et al. 2006). It has been indicated that melatonin, either by gut mobilization (exogenous form) or in response to the precursor, tryptophan (an endogenous form), increases the rate of healing of chronic stomach ulcers, which is associated with an increase in gastric blood flow at the margin of the ulcers, increased plasma gastrin levels and luminal NO release (Brzozowska et al. 2002).

Melatonin and *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is a gram-negative spirobacterium that resides in epithelial gastric cells and gastric mucosal. *H. pylori* infection is associated with chronic gastritis, peptic ulcers, and lymphomas (Akbari et al. 2023). It has been suggested that the use of melatonin is an appropriate candidate for the eradication of *H. pylori*, which is still needed for further studies. TLRs are regulators of regulatory T cells (Treg), which are part of the innate immune system. It has been suggested that by blocking the signaling pathway of TLR4, the expression of the MyD88 decreases, which also leads to a decrease in the activity of the NF-κB (Gong et al. 2016). Because *H. pylori* increases the risk of DNA damage of infected gastric epithelial cells, melatonin also reduces the extent of these injuries with its antioxidant properties (Asghari et al. 2017; Xin et al. 2015). Other controlling molecules involved in the pathogenesis of *H. pylori* infections include Foxp3 and TGF-β1. Studies have shown that *H. pylori*-infected mice have increased the expression of the Foxp3 of Treg cells and increased the IL-10 production of B-cells in the gastrointestinal mucosa. In a study, the presence of melatonin reduced the expression of the Foxp3 and several cytokines through the TLR2 or TLR4 signaling pathway. MyD88 is an adaptor molecule and a downstream factor of the TLR2 and TLR4, and its expression like TLR2 decreases during the two-week treatment with melatonin. In addition, *H. pylori* infections release the specific pro-inflammatory cytokines of the Th1, Th2, and Th17 cells such as IFN-γ, TNF-α, IL-2, IL-6, IL-10, IL-17, and TGFβ1, through TLRs2 and TLR4 signaling pathways. It has been observed that during the treatment of *H. pylori*-infected models with melatonin, the serum level of these pro-inflammatory cytokines has significantly decreased (Luo et al. 2018b).

Melatonin and stomach cancer

Gastric cancer (GC) is the fourth most common cancer and one of the most embryonic malignant tumors with the second-highest mortality rate among all malignancies worldwide (Zhang et al. 2013; Sumei Zhang et al. 2012; Zhu et al. 2018a). Among the risk factors for GC, *H. pylori* infection, nitrites and processed meat products can be mentioned (Zhu et al. 2018a). Common treatments for GC include surgery, radiotherapy, and chemotherapy. Since the treatment period is heavy and the result of the treatment and their survival are

poor, we need more effective, lasting, and safe treatment. Melatonin is a new therapeutic compound for this purpose that has high efficacy and low toxicity (Asghari et al. 2017; Zhang et al. 2012). In most cases, for the treatment of GC, melatonin is used as a complementary therapy along with chemotherapy. Also, immunotherapy with low doses of IL-2 and melatonin has a good effect and tolerance on digestive malignancies, especially GC. A study observed that tumor regurgitation in the subcutaneous injection of IL-2 (in low doses) and melatonin was a biotherapy in patients with metastatic GC (Zhang et al. 2013). Melatonin has also been proven to exert an anticancer activity through its direct inhibitory effect on cell proliferation and metastasis, blockage of growth factor secretion, suppression of tumor cell migration, invasion, and metastasis, inhibition of colony formation, activation of anti-oxidative stress, stimulation of anticancer immune system, and induction of apoptosis of cancer cells (Asghari et al. 2017; Liu et al. 2017; Lissoni et al. 1997; Xin et al. 2015; Zhang et al. 2013; Zhang et al. 2012). The antioxidant properties of melatonin limit oxidative DNA damage, thus reducing carcinogenesis. Also, melatonin induces apoptosis with its pro-oxidant activity in cancer cells, which depends on the condition of NF-κB activation (Asghari et al. 2017). According to studies conducted on GC cells, it has been shown that melatonin affects the MAPK signaling pathway (including p38, JNK, and ERK molecules that control various cellular activities such as metabolism, cell proliferation, migration, and apoptosis), which reduces cell viability, colony formation, and migration and increases apoptosis. Melatonin activates p38, JNK, and ERK by their phosphorylation and, on the other hand, by upregulation of the Bax and downregulation of the Bcl-2. This leads to the activation of caspase-3 in the cancer cells, which ultimately induces apoptosis (Asghari et al. 2017; Li et al. 2015; Xin et al. 2015). Furthermore, it has been shown that melatonin leads to reduced cancer cell proliferation by phosphorylation of p38 and JNK, followed by a decrease in the expression of NF-κB p65 (Asghari et al. 2017). Caspase-3 is an apoptotic regulator, and it has been suspected that this is the final caspase for cell death. Activation of this caspase occurs through the proteolytic cleavage of inactivate procaspase-3 which is converted to active subunits. Melatonin has been shown to increase the caspase-3 level and thereby lead to the induction of apoptosis in gastric cancer cells (Zhang et al. 2013). Other mechanisms of melatonin are blocking growth factors signaling pathways that stop the cell cycle modulating intercellular interactions and destroying cytoskeletal structures, which causes the death of cancer cells. One of the risk factors for carcinogenesis is damage to DNA and mutations that activate oncogenes or inactivate tumor suppressor genes, which ultimately cause excessive cell proliferation and tumor formation. It has been observed that melatonin, by upregulation of p21, as a tumor suppressor gene, causes cell cycle arrest and inhibition of DNA synthesis in GC cells (Asghari et al. 2017). The inhibitory role of melatonin on cancer cell proliferation is applied in two ways: (i) by reducing the synthesis of DNA in cancer cells and (ii) by promoting cell differentiation by upregulation of the endocan gene and reducing the activity of alkaline phosphatase and lactate dehydrogenase (Xin et al. 2015).

Alkaline phosphatase and lactate dehydrogenase are enzymes involved in the differentiation of gastric cells, which increase their activity in gastric cancer. Melatonin exerts its anticancer activity by reducing these enzyme's activities. In addition, the endocan gene, which is a sulfate proteoglycan, is overexpressed in stomach cancer, and melatonin plays a key role in cancer repression by reducing the expression and transcription of this gene (Zhang et al. 2012). The suppression of linoleic acid, an important fatty acid that cancer cells receive through the cAMP signaling pathway, is one of melatonin's other anticancer characteristics. As a result, there will be disruptions in energy generation and the development of cancer cells.

Cancer cell epithelial-mesenchymal transition (EMT) is a process that transforms cancer cells into cancer stem cells that have metastatic and invasive properties (Tangsiri et al. 2024). It has been observed that melatonin inhibits this process in the gastric adenocarcinoma cell line (Bakhtiyari et al. 2023). The weakening of EMT is accompanied by a downregulation of the C/EBPB gene, which decreases NF-κB signaling to β-catenin and suppresses E-cadherin, eventually inhibiting tumor growth and metastasis (Asghari et al. 2017; Zhao et al. 2023a). Moreover, pro-angiogenic markers such as hypoxia, cytokine interleukin-6, MMPs, vascular endothelial growth factor (VEGF), and interleukin-6 that overexpress in GC are associated with cancer cell invasion and progression. VEGF activates several MMPs, including MMP-9 and MMP-2, that cause extracellular matrix destruction, invasion, and angiogenesis. It has been observed that melatonin directly binds to the MMP-9 active site and suppresses this protein function (Asghari et al. 2017; Xin et al. 2015). Melatonin also increases the capacity of DNA repair and regeneration by some of the key genes and inhibits tumorigenesis (Fig. 2) (Xin et al. 2015). Much evidence has shown that malignancies occur due to not only genetic changes but also epigenetic changes, such as microRNA (miRNA) changes that play a key role in tumorigenesis. miRNAs, by targeting downstream genes, cause negative regulation of gene expression through the effect of mRNA transcription and protein translation (Karami Fath et al. 2022). Changes in miRNA expression can suppress tumors and oncogenes at the onset and progression of cancer. Recently, the role of miRNAs has been proven in inhibiting melatonin-induced growth and apoptosis of cancer cells. Mothers against

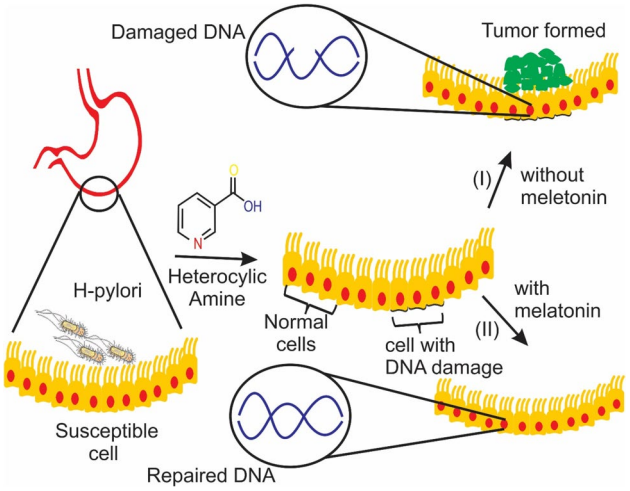

Fig. 2 Effect of melatonin on the capacity of DNA repair and regeneration. *H. pylori* increases the susceptibility of gastric cells to carcinogens and mutagens. (I) Carcinogens like heterocyclic amines in the diet can damage the DNA of normal gastric epithelial cells, which ultimately induces tumorigenicity. (II) In the presence of melatonin, key enzymes involved in DNA repair are induced and increase the capacity for DNA repair. In this way, melatonin prevents tumorigenicity of the gastric cells

decapentaplegic homolog 3 (Smad3) is a key regulator of the TGF-b signaling pathway that regulates cell proliferation, differentiation, and apoptosis. In many cancers, especially GC, an abnormal expression of Smad3 has been observed. It has been proven that miR-424-5p could control the growth and proliferation of GC cells by targeting Smad3. It has been demonstrated that melatonin increases the expression of miR-16-5p in GC. Here, miR-16-5p targets Smad3 to reduce its expression, which in turn regulates the TGF-b signaling pathway, which is crucial for controlling cell proliferation. This prevents the growth of cancer and triggers apoptosis (Zhu et al. 2018a).

On the other hand, the immune system status plays a critical role in the prognosis of cancer patients. Therefore, the inhibition and suppression of chemotherapy-related immunosuppression (such as lymphocyte damage) by melatonin can affect the quality and quantity of patients' lives (Lissoni 2002). Tumors escape the immune system by tolerating immunity or suppressing the immune system. In many cancers, especially GC, tumor cells suppress the antitumor T cells by activating the Treg. Melatonin, with its pleiotropic functions, can control and increase immune responses (Asghari et al. 2017). $CD4^+$ $CD25^+$ T cells are a subset of regulatory T cells that are abundant around the GC tumor and have a direct relationship with the development of this cancer. The function of these cells depends on the Foxp3 protein. In-vitro and in-vivo experiments showed that melatonin decreased the number of $CD4^+$ $CD25^+$ T cells as well as suppressed their regulatory protein expression (Foxp3), thereby reducing tumor volume and weight (Asghari et al. 2017; Xin et al. 2015).

Melatonin and intestinal functions

Studies have up to now demonstrated some of the effects that melatonin appears to have on intestinal function. This research has yielded some fascinating findings, one of which is the synthesis of melatonin in enterochromaffin cells (EC) of intestinal tissue. Specifically, large quantities of melatonin have been observed in colon and rectum tissue (Bertrand et al. 2014; Chojnacki et al. 2012; Poon et al. 1997). It appears that tryptophan stimulates the production of melatonin in the enterochromaffin cells (S. J. Konturek et al. 2007). It has been noted that the intestinal tissue's melatonin content is not just derived from endogenous production; some foods also contain melatonin, which is absorbed by them. Additionally, certain common gut flora bacteria can also produce melatonin, meaning that melatonin from these sources is present in the intestinal lumen (Forsythe et al. 2010; Peuhkuri et al. 2012). Based on several studies, melatonin neutralizes the oxidative effects of GSH-depleting drugs such as menadione and prevents inhibition of calcium uptake by these drugs (Areco et al. 2016; Carpentieri et al. 2014). Some studies have also shown that melatonin inhibits cholesterol absorption in rats (Hussain 2007). The relationship between melatonin and cholecystokinin (CCK) and pancreatic amylase is also interesting. CCK is a hormone that contributes to the absorption of lipids through increasing bile secretion. Melatonin appears to stimulate CCK release via pancreatic amylase, MT2 receptors, and mucosal bicarbonate. It also plays a major role in the slow movement of peristalsis, which facilitates efficient meal absorption (Nawrot-Porabka et al. 2013; Slominski et al. 2012). Moreover, a study on hens showed that melatonin increases the expression and function of amino acid transporters in the small intestine (Liu et al. 2018a). A study on chickens also showed that melatonin enhances not only the intestinal structure but also the digestive function and absorption of the small intestine (Li et al. 2017). Melatonin is also thought to play a role in the secretion of chloride by colon cells in the large intestine (Chan et al. 1998).

Not only does melatonin influence the aforementioned conditions, but it also has an impact on intestinal permeability and motility. Increased intestinal permeability can result in inflammation or leaky gut syndrome. The intestinal mucous membrane, whose strength depends on the tight connections between the epithelial cells, blocks the fast passage of soluble materials and pathogens into the underlying layers. Melatonin strengthens the intestinal membrane, as some studies have shown that melatonin inhibits the effects of alcohol consumption on the increase of permeability in

the duodenum (Sommansson et al. 2013b; Sommansson et al. 2014; Swanson et al. 2015) and probably applies these protective effects through acetylcholine nicotine receptors (Sommansson et al. 2013a). It was also shown that serotonin stimulates intestinal contractions through specific receptors on the surface of cholinergic cells, while melatonin decreases the contractile effects of serotonin; this inhibition effect of melatonin was also shown in rats (Tan et al. 2013; Velarde et al. 2010).

Melatonin's effects on intestinal bacteria and the bacteria's effects on the amount of melatonin

The number of sex hormones, epigenetic modifications, immunological response, biliary function, bile acids, and other physiological processes are only a few of the activities that intestinal bacteria are known to influence, both in health and sickness (Nabi-Afjadi et al. 2023b; Rizzetto et al. 2018; Wu et al. 2017a; Zhang et al. 2023). Furthermore, intestinal bacteria appear to be associated with many human diseases such as lupus, multiple sclerosis, type 1 diabetes, cardiovascular disease, and inflammatory bowel disease (IBD) (Ni et al. 2017; Pouriamehr et al. 2019; Rizzetto et al. 2018; Sharbatdar et al. 2023; Weis 2018; Wu et al. 2017a), and even changing the composition of intestinal bacteria using probiotics is suggested as a therapeutic approach for the treatment of many human diseases (Cho et al. 2018; Liu et al. 2023; Marietta et al. 2018; Tian et al. 2022; Zhao et al. 2023b). It appears that melatonin affects intestinal bacterial composition, as it was shown in a study that melatonin increases the beneficial bacteria called *lactobacillus* in the intestines of rats (Ren et al. 2018). *Lactobacillus* has many beneficial effects, for example, protecting intestinal health, beneficial weight loss, and positive effect on lipid profile (Crovesy et al. 2017; Slover and Danziger 2008; Wu et al. 2017b).

According to a different study, melatonin enhanced lipid metabolism and dramatically decreased the buildup of fat in the intestines of rats fed a high-fat diet by blocking the growth of lactobacillus, lowering the ratio of firmicutes to Bacteroides, and having an effect on the expression of genes related to lipid metabolism (Yin et al. 2018a). Additionally, melatonin alleviated lipid dysmetabolism in animals fed a high-fat diet by changing the gut microbiome. Another study also showed that melatonin inhibits obesity in rats fed with a high-fat diet by decreasing the ratio of firmicutes/Bacteroides, as well as the increase of bacteria called akkermansia contributing to mucosal health (Xu et al. 2017). As stated, oral melatonin reduces the amount of LPS produced by *E. coli*. This, in turn, ameliorated the transcriptional inhibition of angiopoietin-like 4 (ANGPTL4) induced by NFIL3 through the ileum's toll-like receptor 4 (TLR4)/interleukin-22 (IL-22)/STAT3 signaling, improving ileal lipid intake and reducing the accumulation of fat in epididymal-WAT. In addition, melatonin may potentially control energy metabolism through its interaction with microbial metabolites, particularly short-chain fatty acids (SCFA) like butyric acid. Butyrate's actions are partially mediated by activating the melatonergic system, indicating a potential interaction between melatonin and the gut flora. Melatonin's actions seem to be partially mediated by α-7 nicotinic receptors, and the opioid system may be used by butyrate and melatonin to control obesity (Guan et al. 2021). By altering the abundances of Bacteroides and Alistipes, melatonin can help prevent lipid metabolic diseases through the microbiota-acetic acid axis pathway. Meanwhile, the gut microbiota will affect muscle composition and metabolism, and the concept of the gut–muscle axis has been formulated (Yin et al. 2018b). In another study on mucosal colitis, melatonin was associated with an increase in the ratio of firmicutes/ Bacteroides (Zhu et al. 2018b). These results imply that the makeup of gut bacteria is affected differently by melatonin, depending on the situation. This provides an intriguing regulation mechanism that will likely be clarified by further research.

However, the amount of melatonin can also be impacted by intestinal bacteria. The organelles called mitochondria are exclusive to eukaryotic cells. These organelles have an α-proteobacterial ancestor as their parent organism. According to the idea of endosymbiosis, α-proteobacteria invaded the progenitors of eukaryotes 1.5–2 billion years ago. These bacteria are capable of aerobic respiration and produce far more ATP for the host's consumption than could be produced by glycolysis thanks to an electron transport chain that increases a proton potential (Tan and Hardeland 2020). Tan. D. et al. proposed the theory that gut bacteria are capable of producing melatonin for the first time (Tan et al. 2023). Melatonin, which is produced by yeast, has been found in the wine in this line (Morcillo-Parra et al. 2019). Furthermore, alkylamine N-acetyltransferase (AANAT) has been found in archaea and cloned from them (Lee et al. 2022). A large number of species from these basic groups make up the gut microbiota. Consequently, there is no reason to deny that the host's gut bacteria serve as an additional source of melatonin. Melatonin produced by microbiota primarily serves to shield its hosts from environmental assaults, especially free radicals (Luo et al. 2018a). For instance, under aluminum stress, recombinant *E. coli* with melatonin synthesis enzymes produce eight times as much melatonin as the wild type, and as a result, their survival rate increases 100 times above that of the WT (Luo et al. 2018a). Furthermore, melatonin produced by the microbiota may help strengthen the host's defenses. On the other hand, because of the incredibly high levels of bile melatonin in humans and other animals, melatonin from microbiota penetrates the host's system. Different species' bile contains

melatonin in quantities ranging from 2000 to 11,000 pg/mL, which is 2–3 orders of magnitude more than that of daytime serum. It is probable that the bulk of the melatonin in the bile is derived from microbiota, which enters the enterohepatic circulation and is then expelled into the bile (Reiter et al. 2017). Ouyang et al. also noted that melatonin was detected in cow rumen fluid, where it had a diurnal pattern in the in vivo investigation. The melatonin circadian rhythm was maintained when the rumen fluid was grown in vitro (Ouyang et al. 2021). The findings imply that, although being rhythmic, the melatonin was produced by the rumen bacteria as opposed to the host cell.

Melatonin and irritable bowel syndrome

The intestinal condition known as irritable bowel syndrome (IBS) is typified by symptoms including diarrhea, constipation, bloating, and/or stomach discomfort. Although the precise origin of IBS is still unknown, several theories include the existence of subclinical inflammation and, in particular, the disturbance of the brain-gut axis (Luo et al. 2022; Soares 2014; Zhang et al. 2023). There is some evidence of a positive effect of melatonin in relieving IBS symptoms. A study has shown that patients with sleep disturbance show more severe signs of some of the symptoms of IBS (Chen et al. 2011). Another study showed that prescribing 3 mg melatonin at bedtime did not have an effect on the improvement of sleep disorders in patients with IBS, but significantly reduced abdominal pain in these patients (Song et al. 2005). Another study on post-menopausal women with IBS showed that prescribing 3 mg of fasting melatonin and 5 mg of melatonin at bedtime after a six-month period reduced the severity of IBS symptoms in 70% of patients (Chojnacki et al. 2013). More interestingly, it appears that melatonin agonists also significantly reduce the severity of abdominal pain (Chen et al. 2014). Melatonin is probably also involved in the positive effects of probiotics in reducing the severity of IBS symptoms, as shown by the fact that VL # 3 probiotic use for six weeks reduces the severity of IBS symptoms and increases the level of melatonin in the morning (Didari et al. 2015; Wong et al. 2015). More research is needed to fully understand how melatonin lessens the intensity of symptoms in IBS patients, but since serotonin is positively correlated with the intensity of abdominal pain in IBS patients, it is likely that many of these effects are caused by melatonin's modification of serotonin's effects (Cremon et al. 2011).

Melatonin and inflammatory bowel disease

One organic intestinal ailment is called inflammatory bowel disease (IBD). The symptoms of this inflammatory condition include diarrhea, rectal discomfort, and stomach pain. In vitro investigations show that the levels of inflammatory markers have increased (Moein et al. 2017; Moein et al. 2018). Several factors are involved in the pathogenesis of this disease, including genetic predisposition, intestinal bacteria, and oxidative stress (Abraham and Cho 2009; Molnar and Annaházi 2014; Tuzun et al. 2002). In this disease, the mucosal barrier disorder results in the intrusion of intestinal bacteria into the intestinal lamina propria, resulting in subsequent immune responses leading to chronic inflammation (Abraham and Cho 2009; Moein et al. 2017; Moein et al. 2018; Molnar and Annaházi 2014). The relationship between melatonin and IBD has been the subject of many studies, and interesting findings have been obtained from these studies. In a study conducted on rats with acetic acid-induced colitis, it was shown that exposure to dark environments for two weeks reduced the severity of intestinal injuries (Cevik et al. 2005). In another study on colitis rats' models, it was shown that melatonin decreased the severity of intestinal inflammation. It was also shown that the serum level of melatonin in rats with colitis is higher than the healthy rats. Researchers have suggested that this increase may be due to increased intestinal production of melatonin in response to oxidative stress in colitis rat models (Pentney and Bubenik 1995). A recent study on human specimens has also shown that the level of melatonin-synthesizing enzyme in the colon tissue of IBD patients is significantly high, suggesting an increase in intestinal production of melatonin following the inflammatory process (Chojnacki et al. 2018).

However, another study on IBD patients found that serum levels of melatonin were lower in these patients compared to healthy subjects. There was also no correlation between serum levels of melatonin and inflammatory markers, but there was a direct correlation between serum folate levels and melatonin, which is interesting. It was also shown that serum homocysteine level in IBD patients was increased compared to healthy subjects, and there was a reverse correlation between serum levels of melatonin and homocysteine, which was not statistically significant (Chen et al. 2012), however, considering that homocysteine is a known risk factor for cardiovascular disease, and in addition to IBD, it has been reported to increase in some other human diseases (Ebrahimpour et al. 2018; Goldstein et al. 2004; Montalescot et al. 1997). Further investigation on this correlation with more studies and identifying the effects of Circadian rhythms on the level of homocysteine can be very interesting. Studies on the effects of melatonin on IBD are not limited to the mentioned cases above, as some studies have shown the antioxidant and anti-inflammatory properties of melatonin and have shown positive effects on these properties. Studies conducted on rats with colitis showed that melatonin reduced MDA, nitric oxide, IL6, and TNFα and increased superoxide dismutase and glutathione (Bai et al. 2022; Mei et al. 2005; Tahan et al. 2011). Studies on human

specimens also suggest an increase in oxidative markers, such as MDA, in the serum of IBD patients, suggesting oxidative stress in these patients (Vaghari-Tabari et al. 2018; Vaghari Tabari et al. 2017); moreover, the role of cytokines such as IL6 and TNFα in the pathogenesis of IBD is central (Abraham and Cho 2009). Therefore, it is not surprising that melatonin, with its antioxidant and anti-inflammatory properties, reduces the severity of the disease in IBD patients and is suggested as an effective therapeutic approach (Chojnacki et al. 2011; Li et al. 2008; Liu et al. 2017). It appears that short-term prescribing of melatonin has produced this beneficial effect, and its long-term prescribing not only does not have a positive effect on reducing the severity of the disease but also worsens the severity of inflammation in mouse colitis models. In addition, melatonin agonists appear to be unable to mimic the anti-inflammatory effects of melatonin (Marquez et al. 2006; Zielinska et al. 2016).

There appears to be a relationship between melatonin and serotonin in IBD, as shown in recent studies on colitis models and intestinal mucosal of patients with IBD (Wu et al. 2023). It seems to reduce the availability of melatonin, decrease the activity of tryptophan hydroxylase 1, increase the availability of serotonin in the intestines of mice, and increase the serotonergic cells in the ileum of IBD patients (Giuffrida et al. 2018; MacEachern et al. 2018). Furthermore, serotonin appears to increase the severity of inflammation in mucosal colitis by increasing the expression of MMP-3 and MMP-9 (Chen et al. 2016). In addition, in a study conducted on colon cells, TGF-β, a cytokine with protective effects on the mucus of the intestine, was shown to increase the expression of serotonin transporter (SERT) (Nazir et al. 2015). According to these findings, it is probable that the beneficial effects of melatonin on reducing the severity of inflammation in IBD are due to its role in regulating serotonin function, a possibility that will undoubtedly be further explored by future studies (Table 1).

Melatonin and colorectal carcinoma

Colorectal cancer is the third most common cancer in the USA and has a high mortality rate (Siegel et al. 2017). Circadian rhythm disorder appears to contribute to the pathogenesis of this cancer, and some studies have reported the circadian rhythm disorder as a risk factor for colorectal cancer (Mazzoccoli et al. 2014; Wood et al. 2010). In a study, it was also shown that the effects of physical exercise against colorectal cancer are dependent on the proper activity of the pineal gland, and pineal gland disorder enhances the extent of DNA damage in the colon epithelial cells of rats (Frajacomo et al. 2015). MT1 receptor expression in colorectal cancer cells is also believed to be reduced (Nemeth et al. 2011), all of which suggest the possibility of the anticancer role of melatonin. The beneficial effects of melatonin on colorectal cancer treatment have been reported in several studies. The role of melatonin in inhibiting the proliferation of colorectal cancer cells has been shown in one of these studies (Garcia-Navarro et al. 2007). Furthermore, melatonin appears to induce apoptosis in cancerous cells (Chuffa et al. 2016). One of the approaches to effectively treat cancer is using compounds that could stimulate apoptosis in cancer cells, and melatonin appears to be beneficial in this regard. Recent studies have shown that melatonin can induce apoptosis in colorectal cancer cells through the inhibition of prion proteins in cells that have anti-apoptotic activity and increase the susceptibility of these cells toward oxaliplatin (Lee et al. 2018a; Westergard et al. 2007; Yun et al. 2018). Some studies have also shown that melatonin, via increasing the expression of sodium-calcium exchanger1 (NCX1), reduces calcium levels, induces ER stress, and subsequently induces apoptosis in colorectal and ovarian cancer cells (Chovancova et al. 2017). Some studies also suggest the beneficial effects of melatonin in increasing the susceptibility of colorectal cancer toward 5-fluorouracil and doxorubicin (Fic et al. 2017; Lee et al. 2018b; Pariente et al. 2018). The effect of melatonin appears to increase the susceptibility of colorectal cancer cells toward 5-fluorouracil due to its role in inhibiting the NF-κB and PI3K/AKT signalingpathways (Gao et al. 2017a, 2017b) as very important signaling pathways in cancer progression. In addition, melatonin suppresses angiogenesis in colorectal cancer cells by inhibiting HIF1α (Park et al. 2010). According to the findings, melatonin and some of its metabolites, such as 2-hydroxy melatonin, which has even stronger antitumor effects than melatonin (Yang et al. 2017b), can be effectively utilized in colorectal cancer, and further studies will probably focus more on this issue.

The role of melatonin in liver

The liver is a necessary organ of the body that plays numerous functions including nutrient storage, metabolic functions, excretory functions, digestive functions, fresh molecules synthesis, and detoxification (Chojnacki et al. 2017; Nieminen et al. 2001; Zhang et al. 2017). Regarding the importance of the liver in the body, liver dysfunction can affect human health (Pan et al. 2006; Sheen et al. 2016). Importantly, several studies investigated the melatonin effects on a wide spectrum of liver injuries and diseases including alcoholic liver disease (ALD), non-alcoholic liver diseases, such as non-alcoholic fatty liver diseases (NAFLD), and non-alcoholic steatohepatitis (NASH), hepatic cholestasis, hepatitis, fibrosis, and cirrhosis (Zhang et al. 2017). MT1 and MT2 are melatonin receptors in the liver of mammals. The exact biological function of hepatic melatonin receptors is mostly unclear (Mathes 2010; Mathes

Table 1 Crosstalk between melatonin and IBS, colitis, IBD, and colorectal carcinoma (CRC)

Type of disease	Total number of subjects	Subjects	Dose of melatonin	Duration of treatment	Effects of melatonin/effect of different materials on melatonin	Ref
IBS	40	IBS patients with sleep disturbances/a randomized, double-blind, placebo-controlled study	3 mg at bedtime	2 weeks	Melatonin significantly decreased abdominal pain and attenuated rectal pain sensitivity without improvements in sleep disturbance or psychological distress	(Song et al. 2005)
IBS	70	IBS patients/a double-blind placebo-controlled study	3 mg	8 weeks	IBS scores were significantly higher. After treatment with melatonin relative to placebo. Furthermore, the mean of sleep, anxiety, and depression scores were similar with either melatonin or placebo treatment	(Lu et al. 2005)
IBS	80	Post-menopausal women: first group: patients with IBS with constipation-predominant second group: patients with IBS and with diarrhea-predominant	3 mg fasting/5 mg at bedtime	6 months	6-Sulfatoxymelatonin (6-HMS) level urine was measured in μg/24 h. IBS with diarrhea-predominant group was higher than control and IBS with constipation-predominant groups. Moreover, its levels in the control group were higher as compared to IBS with constipation-predominant individuals. Besides, there was a positive and negative correlation between values of symptoms score and contrary excretion of 6-HMS including IBS-D and IBS-C, respectively	(Chojnacki et al. 2013)

Table 1 (continued)

Type of disease	Total number of subjects	Subjects	Dose of melatonin	Duration of treatment	Effects of melatonin/effect of different materials on melatonin	Ref
IBS	42	IBS patients/a randomized double-blinded placebo study	VSL#3 (a probiotic)	6 weeks	This probiotic, VSL#3, improved symptoms and elevated rectal pain thresholds. Symptom improvement associated with an increase in salivary morning melatonin	(Wong et al. 2015)
IBS	67	IBS patients: (I) patients with constipation-predominant (C-IBS), (II) patients with IBS and with diarrhea predominant (D-IBS)	-	-	6-HMS as a main melatonin metabolite was measured. The 6-SMLT/creatinine ratio was lower in C-IBS and D-IBS groups relative to healthy individuals. The 6-SMLT/creatinine status in women with C-IBS was greater than in men with C-IBS	(Radwan et al. 2009)
IBS	18	IBS patients/randomized, double-blind, placebo-controlled study	3 mg at bedtime	8 weeks	The melatonin significantly improved the overall IBS score. Besides, the post-treatment overall extra colonic IBS score was markedly decreased	(Saha et al. 2007)
Colitis	6–8 mice in each group	Dextran sodium sulfate (DSS)-induced colitis in mice	150 pg/kg	7 weeks	The melatonin administration decreases the severity of DSS-induced colitis in mice. Furthermore, the serum melatonin concentrations were significantly increased in mice that received DSS	(Pentney and Bubenik 1995)
Colitis	Five groups: (I) control, (II) model group, (III) melatonin group, (IV) treated intracolonically with saline, (V) saline and melatonin	Rat colitis is established intracolonically with trinitrobenzene sulphonic acid (TNBS) and ethanol	2.5 mg/kg, 5.0 mg/kg, 10.0 mg/kg	21 days (one a day)	TNBS/ethanol-induced colitis is controlled by melatonin. Besides, it decreased the colon injury and reduced the myeloperoxidase activity. Consequently, it exerts potent anti-inflammatory impacts	(Mei et al. 2005)

Table 1 (continued)

Type of disease	Total number of subjects	Subjects	Dose of melatonin	Duration of treatment	Effects of melatonin/effect of different materials on melatonin	Ref
Colitis	32	Ulcerative colitis (UC) model induced by acetic acid in rats	100 mg/kg/day melatonin	4 weeks	The melatonin repressed colonic mucosal injury in the AA-induced colitis group. Furthermore, melatonin resulted in reduced TNF-a, IL-1b, IL-6, MPO, and MDA levels and increased GSH and SOD levels	(Tahan et al. 2011)
Colitis	Mice (6–8 per group)	Mouse model of TNBS-induced colitis	4 mg/kg	Twice daily from day 1–day 3	The melatonin significantly decreased colitis, ulcer score, and MPO activity in mice	(Zielińska et al. 2016)
IBD	64	Patients with left-sided UC	5 mg daily at bedtime	12 months	It was shown that there were not any significant differences between the level of anxiety and intensity of depression between the patients treated with melatonin and those receiving a placebo. Hence, adjuvant melatonin therapy may help in sustaining remission in patients with UC	(Chojnacki et al. 2011)
IBD	72	The rat colitis model was established by TNBS	2.5 mg/kg, 5.0 mg/kg, 10.0 mg/kg	-	Melatonin decreased colonic lesions improved colitis symptoms and reduced the protein and mRNA expressions of IL-8 and monocyte chemoattractant protein significantly in colon tissues of rats with colitis	(Li et al. 2008)

Table 1 (continued)

Type of disease	Total number of subjects	Subjects	Dose of melatonin	Duration of treatment	Effects of melatonin/effect of different materials on melatonin	Ref
IBD	30	8-week-old mice with colitis induced by dextran sodium sulfate (DSS)	0.2 mg/mL	8 days	The melatonin had a reduction in weight loss, expression of colonic IL-17, and disease index induced by DSS treatment. Moreover, melatonin highly increases the serum status of amino acids	(Liu et al. 2017)
IBD	80	Dinitrobenzene sulfonic acid-colitis in Sprague–Dawley rats	15 mg/kg	-	The melatonin-reduced DNBS-induced colon injury in rats is related to a reduction in activities and expression of proMMP-9 and MMP-2	(Esposito et al. 2008)
CRC	-	SNU-C5/WT colon cancer cells	0–1 mM	Different periods (0–24 h)	Melatonin inhibits cell viability via excessive production of superoxide and increased PrP^{C} expression in CRC cancer cells	(Yun et al. 2018)
CRC	-	Human colorectal adenocarcinoma HT–29 cells	1 mM	24 h	The melatonin significantly increased the cytotoxic effects of 5-FU in HT-29 cells. In addition, melatonin strengthens 5-FU-stimulated cytotoxicity and apoptosis	(Pariente et al. 2018)
CRC	-	LoVo (colon cancer cells sensitive to doxorubicin) and LoVoDX ((colon cancer cells resistant to DOX)	0.1 mM or 1.0 mM	20 min–24 h	MLT intensified the cytotoxicity effect of DOX in the LoVoDX cells. MLT and DOX cause an increase in the percentage of cells expressing P-glycoprotein, which associates positively with the expression of ABCB1	(Fic et al. 2017)

Table 1 (continued)

Type of disease	Total number of subjects	Subjects	Dose of melatonin	Duration of treatment	Effects of melatonin/effect of different materials on melatonin	Ref
CRC	-	Human colon cell lines SW620 and LOVO	1 mM	48 h	Melatonin synergized the chemotherapeutic effect of 5-FU to suppress the growth of colon cancer by increasing the anti-proliferation, anti-migration, and pro-apoptotic activities. Moreover, it synergized the antitumor effect of 5-FU by targeting the PI3K/AKT and NF-κB/iNOS signaling	(Gao et al. 2017a, 2017b)
CRC	-	Human colorectal carcinoma cell line HCT 116	0–2 mM	0 h, 24 h, 48 h, or 72 h	Melatonin inhibited HCT 116 cellular proliferation, colony formation rate, and cell migration counts following IR. Increasing the radio sensitivity of CRCs by melatonin was found to be associated with cell cycle arrest in the G2/M phase, down-regulation of proteins involved in DNA double-strand break repair, and apoptosis	(Wang et al. 2018a)

et al. 2008). It is suggested that hepatic melatonin receptors may be implicated in the regulation of blood glucose (Mathes 2010; Muhlbauer et al. 2009). Melatonin could decrease liver injuries and diseases by suppressing oxidative injury, improving mitochondrial physiology, inhibiting liver neutrophil infiltration, and the reduction of apoptosis rate (Mauriz et al. 2007; Zhang et al. 2017). Among them, the antioxidant and anti-inflammatory effects of melatonin have become more prominent (Zhang et al. 2017). The detoxification of many molecules by the liver leads to the production of ROS which, in turn, results in oxidative damage in hepatocytes. So, via its antioxidant properties, a high level of melatonin in the liver can preserve this important organ (Mortezaee and Khanlarkhani 2018). Key antioxidant melatonin acts both directly on mitochondria, where it reduces the production of ROS, and indirectly on the body by promoting the activity of the endogenous antioxidant system, which includes GSH, SOD, GPx, glutathione reductase (GSR), and suppressing pro-oxidant enzymes like NOS and lipoxygenases (Bonomini et al. 2018; Mathes 2010; Murawska-Ciałowicz et al. 2010; Subramanian et al. 2007). To highlight melatonin's direct antioxidant effect, consider that oxidative phosphorylation—the process by which mitochondria produce energy—is the main job of the mitochondria. Superoxide, the most prevalent ROS, is created when some electrons from the electron transport chain unavoidably escape during this process and combine with oxygen. Superoxide can then be transformed into other reactive species. Most of the time, the mitochondrial antioxidant system carefully regulates the amount of ROS present and keeps them within a range that allows them to function as signaling molecules. If not, high amounts of ROS cause oxidative stress, which damages tissue and cells (Reiter et al. 2017). It should be noted that melatonin is one of the important antioxidants that protect mitochondria from ROS/oxidative stress. It has been discovered that the mitochondria of many species, including plants and animals, contain melatonin-synthesizing enzymes. It has been revealed that the melatonin production mitochondrial location is restricted to the matrix. The mitochondrial matrix is the best location for melatonin synthesis in terms of substrate availability (Quintela et al. 2018; Tan and Hardeland 2020). A cofactor for melatonin synthesis called acetyl coenzyme A (acetyl-CoA) is mostly produced in mitochondria at a concentration that closely matches the Km of AANAT, the enzyme that limits the pace at which melatonin synthesis occurs (Agrimi et al. 2004). S-adenosylmethionine (SAM), which supplies the methyl group for melatonin synthesis catalyzed by the enzyme acetylserotonin methyltransferase (ASMT), is another significant substrate for melatonin production. The concentration of SAM in mitochondria is consistently higher than in other cellular compartments (Chen et al. 2023; Tan et al. 2016). Significantly, mitochondria have higher melatonin levels than the cytoplasm. Melatonin's action on mitochondria is primarily responsible for its protective properties (Berger et al. 2019). Mitochondrial dynamics is the term for the periodic fission and fusion cycles of mitochondria. Fusion often increases the size and functionality of mitochondria. Fission boosts the quantity of mitochondria and is essential for cell division. Fission, however, serves the purpose of separating the defective mitochondrial segments from the healthy ones in post-mitotic cells. The broken, defective segments go through a process called mitophagy, which is an autophagic process (Berger et al. 2019; Fang et al. 2020; Li et al. 2023; Luo et al. 2022). The majority of the time, melatonin increases the activity of mitochondrial complexes 1, 3, and 4, balances the potential of the mitochondrial membrane, shortens the time that the mitochondrial membrane permeability transition pore (mtPTP) opens, and sustains ATP production. All of these processes help to keep the mitochondria in their functional state (Fang et al. 2020; Fernández Vázquez et al. 2018).

As an example of the indirect antioxidant action of melatonin, it was shown that the 2.5 mg/kg, 5 mg/kg, and 10 mg/kg doses of melatonin augmented SOD and GSH-Px activities, and the 10 mg/kg dose of melatonin decreased the levels of malondialdehyde (MDA) in the liver of NAFLD rats stimulated by a high-fat diet (HFD). Consequently, melatonin has protective activity in NAFLD, likely via its antioxidant properties (Pan et al. 2006). Jang et al. also evaluated melatonin effects on IL-6-induced different hepatic inflammatory responses in HepG2 cells. They showed that melatonin diminishes inflammatory responses such as a decrease of the multidrug resistance-associated protein (MRP2) expression stimulated by IL-6, reduction of albumin production, enhanced hepcidin expression, decreased glycogen storage, and reduced functions of mitochondria (Jang et al. 2018). Additionally, a recent study found that in patients with non-alcoholic fatty liver disease (NAFLD), melatonin lowers the levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α as well as some markers of fat metabolism, including gamma-glutamyltransferase (GGPT) activity, aspartate aminotransferase, alkaline phosphatase, triglyceride levels, and low-density lipoprotein (LDL)-cholesterol (Celinski et al. 2014). Furthermore, in HFD-induced hyperlipidemia, melatonin increased the relative hepatic carnitine palmmitoyltransferase-1α expression and markedly decreased the activities of the hepatic lipogenic enzymes, such as SREBP1c, fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD1), acetyl-CoA carboxylase (ACC), and PPARγ (Ou et al. 2019).

So, melatonin plays an important role in the modulation of several metabolic processes including lipid metabolism, insulin sensitivity, glucose metabolism, and body weight (Mi et al. 2018; Sun et al. 2016). In this regard, Sun et al. examined the effects of melatonin on NAFLD induced by HFD in

C57BL/6 mice. In addition to a marked decrease in TNF-α, IL-1β, and IL-6 expression, treatment with melatonin leads to the reduction of body weights and liver weights, fasting plasma glucose, alanine transaminase, and low-density cholesterol in the HFD mice by the suppression of mitogen-activated protein kinase (MAPK)-JNK/P38 signaling pathway (Sun et al. 2016). A growing body of evidence supports that the AMP-activated protein kinase (AMPK) has a critical function in lipid metabolism. The activation of AMPK leads to the inactivation of acetyl-CoA carboxylase (ACC), a liver enzyme that plays a serious role in fatty acid synthesis and oxidation (Serviddio et al. 2013; Wu et al. 2023). Besides, AMPK modulates the gene expression of transcription factors associated with lipid metabolism regulation such as peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs) that are involved in lipolysis and lipogenesis, respectively (Mi et al. 2018; Serviddio et al. 2013). Interestingly, it is reported that melatonin may inhibit oleic acid-induced lipid accumulation in HepG2 cells through the upregulation of AMPK (Mi et al. 2018). Moreover, the administration of melatonin not only reduced serum total cholesterol and LDL-cholesterol but also increased high-density lipoprotein (HDL)-cholesterol in hypercholesterolemic rats stimulated by diet. Furthermore, lipid peroxidation (LPO) in the liver membrane is suppressed by melatonin (Hoyos et al. 2000). The regulation of carbohydrate metabolism in hepatocytes is one of the most crucial melatonin effects. However, there are contradictory results regarding the effect of melatonin on carbohydrate metabolism (Akmali et al. 2010; Poon et al. 2001; Wang et al. 2022). Poon et al. have reported that melatonin may elevate the plasma glucose level via its direct action on the liver (Poon et al. 2001). Whereas, a recent study showed that melatonin alleviates plasma glucose and can enhance hepatic glucokinase, hexokinase, and glucose 6-P dehydrogenase (G6PD) activities, the insulin receptors on hepatocyte membranes and as well as increasing the release of insulin by the pancreatic β-cells (Akmali et al. 2010). The mechanism by which melatonin regulates blood glucose is still unclear. It is suggested that melatonin may enhance hepatic glycogen synthesis through the modulation of the PKCzeta-Akt-GSK3beta pathway to reduce blood glucose. Therefore, melatonin may be a promising strategy for the treatment of diabetes (Shieh et al. 2009).

Bile, as a pivotal physiological fluid, plays important roles in cholesterol metabolism regulation, the stimulation of lipid absorption, and the elimination of toxic substances from the liver. It has been proven that there is a high amount of melatonin in the bile which can preserve biliary and small intestinal epithelium against oxidative damage (Glaser et al. 2014; Tan et al. 1999). Interestingly, melatonin increases the production of bile in a dose-dependent manner (Vairetti et al. 2005). Several studies have revealed that melatonin can be an encouraging anticancer treatment (Mortezaee 2018; Su et al. 2017). Apoptosis resistance is one of the most important factors associated with hepatocarcinogenesis. Melatonin restrains apoptosis resistance and induces apoptosis in HCC (Mortezaee 2018). Noticeably, melatonin can increase endoplasmic reticulum (ER) stress-induced apoptosis in HCC cells via the blocking of activating transcription factor 6 (ATF-6) and cyclooxygenase-2 (COX-2) expression (Bu et al. 2017). In recent years, the regulatory relationship between melatonin and non-coding RNAs in cancer has been one of the hot research topics (Chen et al. 2018a; Wang et al. 2018b; Wang et al. 2017). Melatonin therapy (at 1 mM and 2 mM doses) represses the proliferation, migration, and invasion and also promotes the let7i-3p microRNA expression in HepG2 cells. Besides, the let7i-3p, as a tumor suppressor, decreases the expression of RAF1 and the activation of its downstream oncogenic MAPK signaling pathway. Hence, melatonin inhibits the HCC development by miRNA Let7i-3p-mediated RAF1 downregulation (Wang et al. 2018b). Melatonin also leads to the upregulation of long non-coding RNA-CPS1 intronic transcript 1 (lncRNA-CPS1-IT1) expression via the induction of FOXA2 expression in HCC cells. This increase in lncRNA-CPS1-IT1 expression resulted in the reduction of HIF-1α activity, thereby suppressing the progress of epithelial-mesenchymal transition (EMT) and HCC metastasis (Chen et al. 2018b; Wang et al. 2017; Zalpoor et al. 2022a, 2022b). Melatonin can enhance the sensitivity of HCC cells to chemotherapy by the suppression of the DNA repair capacity of HCC cells. The mechanism by which melatonin represses DNA repair processes is through the overexpression of lncRNA RAD51-AS1, which binds to RAD51 mRNA to decrease the expression of RAD51 protein. The RAD51 protein binds to single-stranded DNA to provoke homologous recombination (HR) to complete DNA repair (Chen et al. 2018a) (Fig. 3). Taken together, melatonin with diverse pleiotropic actions can be used as a promising choice for the treatment of liver diseases (Table 2).

Melatonin and pancreas

Melatonin has several biochemical effects on the pancreas. At first glance, the effects of melatonin on β cells, insulin secretion, and glucose metabolism are of particular importance. To justify the multiple effects of melatonin, we must pay attention to the distribution of MT1 and MT2 (Pandi-Perumal et al. 2008). Based on multiple research, MT1 and MT2, respectively, are more localized to α-cells and β-cells (Nagorny et al. 2011). The fundamental results of the melatonin impact on these receptors are that the loss of both melatonin receptors leads to a significant increase in insulin secretion. Melatonin inhibits the secretion of insulin in

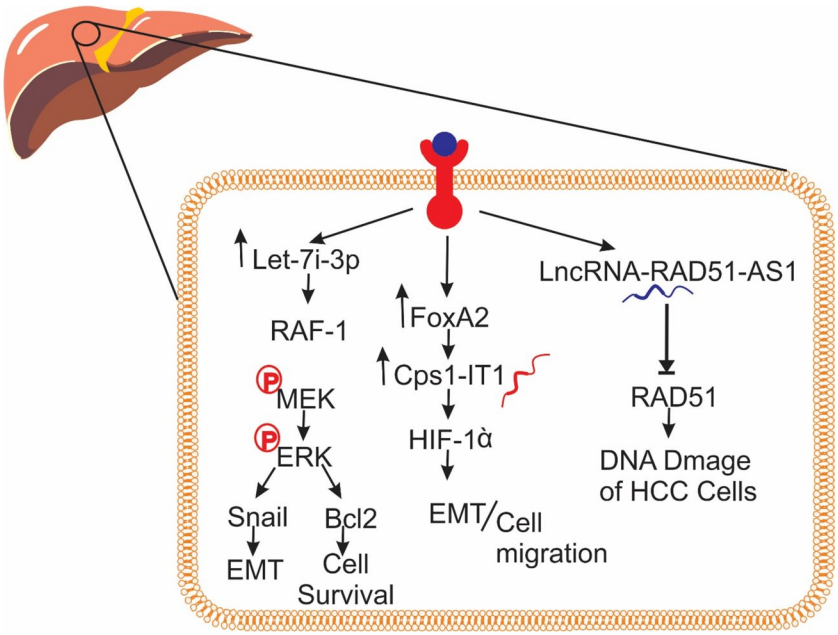

Fig. 3 Melatonin can inhibit the progression of HCC by the regulation of non-coding RNA expression. Melatonin induces the expression of let7i-3p and thereby represses RAF1 and its downstream oncogenic pathway. Melatonin also reduces EMT progression and HCC metastasis through the induction of FOXA2 and CPS1-IT1 expression and inhibition of HIF-1α nuclear translocation. In addition, melatonin suppresses the DNA repair capacity of HCC cells through lncRNA RAD51-AS1-mediated the suppression of RAD51 expression

pancreatic β-cells through G-protein-coupled MT1 receptor and cyclic guanosine monophosphate receptors (cGMP via M2 dependent receptor). This results in the downregulation of adenylate cyclase and guanylyl cyclase activity, which in turn lowers the levels of cAMP and cGMP as second messengers, which in turn subsequently reduces the levels of protein kinase A (PKA) and protein kinase G (PKG). Conversely, a number of investigations have demonstrated the role of inositol 1,4,5 triphosphate (IP3) in the melatonin signaling pathway and, therefore, the production of insulin from pancreatic β-cells (Espino et al. 2011; Peschke et al. 2007). Based on recent research, the secretion and synthesis of melatonin are very different in type 1 and type 2 diabetes. At an early stage of type 2 diabetes, increasing insulin secretion leads to decreased melatonin secretion in the pineal gland. In this situation, the protective effect of melatonin on β-cells is diminished and increased incidence of diabetes during life. In contrast, during type 1 diabetes, insulin secretion considerably decreased, and after that, melatonin secretion by the pineal gland significantly increased (Jaworek et al. 2012). The Langerhans pancreatic islets have low antioxidant capacity; hence, ROS and reactive nitrogen species (RNS) may contribute to the dysfunction of β-cells and subsequently impaired insulin secretion during type 2 diabetes. Since melatonin has protective effects on these cells, ischemia/reperfusion (IR), which happens during tissue transplantation and other pathological conditions, is another way that the pancreas might generate excessive ROS. IR-caused acute pancreatitis by causing inflammatory infiltrates to build up. Administration of melatonin in these subjects has powerful antioxidant effects by reduction of free radical-derived such as MDA and restoration of antioxidant factors such as CAT and GPx (Espino et al. 2011; Muñoz-Casares et al. 2006). By reducing pro-inflammatory cytokines like IL-1β, IL-6, IL-8, and TNF-α and increasing anti-inflammatory cytokines like IL-10, melatonin also lessens the severity of pancreatitis by modulating the immune system. Additionally, melatonin can increase heat shock protein and reduce apoptosis and necrosis, both of which shield the cell compartment from damage (Jaworek et al. 2012; Nabi-Afjadi et al. 2021; Nabi-Afjadi et al. 2023a). Patients with obesity taking melatonin for 12 weeks also showed a pronounced decrease in the insulin resistance (IR) index. In the case of existing IR, melatonin treatment improves glucose metabolism in the IR model by restoring the effect of insulin on the cardiovascular system (Song et al. 2018). A link between the polymorphisms of the melatonin receptor genes and IR has also been brought to light. Melatonin participates in improving IR via melatonin receptor 1 (MT1) or by preventing mitochondrial dysfunction, promoting endoplasmic reticulum (ER) stress, and improving hepatokines associated with IR and T2DM, such as alpha-2-HS-glycoprotein (Guan et al. 2021; Su et al. 2023; Sun et al. 2018).

Melatonin and appetite

Circadian rhythm as an environmental synchronizer has an important role in the control of animal behavior; adjustment of body energy balance is dependent on the correlation between the central nervous system, neuro-anatomical network, and environmental conditions. This biological system integrates information from the body's energy status and environmental conditions (Helwig et al. 2009).

Table 2 Hepatoprotective effects of melatonin

Subjects	*Melatonin doses*	*Hepatoprotective effects of melatonin*	*Reference*
HepG2 cells	0.1–0.3 mM	Melatonin inhibited TG and cholesterol increased and down-regulated ACC, FAS, and SCD1, and also, it upregulated the CPT1 expression in HepG2 cells with lipid accumulation induced by oleic acid	Mi et al. (2018)
HepG2 cells	1 nM	Melatonin decreased IL-6-induced inflammatory responses such as a decrease of the MRP2 expression, reduction of albumin production, enhanced hepcidin expression, decreased glycogen storage, and reduced functions of mitochondria	Jang et al. (2018)
C57BL/6 mice	10 mg/kg	Treatment with melatonin led to the reduction of body weights and liver weights, fasting plasma glucose, alanine transaminase, and low-density cholesterol in HFD-induced NAFLD in C57BL/6 mice	Sun et al. (2016)
Rat	10 mg/L in the drinking water	Melatonin administration decreases total cholesterol and LDL-cholesterol and stops the reduction of HDL-cholesterol in diet-induced hypercholesterolemic rats. There were not any effects on the levels of cholesterol or TG. In addition, melatonin administration reduced serum uric, and bilirubin enhanced serum glucose levels	Hoyos et al. (2000)
Rat	0.5 mg/kg and 1 mg/kg body weight	Melatonin treatment reduced the levels of cholesterol, phospholipids, TG, and free fatty acids in the liver tissue of rats. The treatment with melatonin improved the liver antioxidant enzymes activity such as SOD, catalase, and GPx, as well as augmented GSH levels	Subramanian et al. (2007)
Rat	2.5 mg/kg, 5 mg/kg, and 10 mg/kg daily	Melatonin reduced the serum levels of alanine aminotransferase, aspartate aminotransferase, and levels of liver total cholesterol and TG in HFD-induced NAFLD rats. Moreover, melatonin enhanced the activities of SOD and GSH-Px and decreased the level of MDA in the liver	Pan et al. (2006)
Rat	10 mg/kg	The cholesterol absorption was reduced by melatonin in rats fed on HCD. Melatonin decreased the plasma levels of total cholesterol, TG, VLDL, and LDL-cholesterol and the contents of cholesterol and TG in the liver and also increased the HDL-cholesterol level	Hussain (2007)
Rat	1.25 mg/mL	Melatonin decreased plasma glucose, cholesterol, and triacylglycerol and augmented hepatic glucokinase, hexokinase, and G6PD activities in streptozocin-induced diabetic rats	Akmali et al. (2010)

TG, triglyceride; *ACC*, acetyl-CoA carboxylase; *FAS*, fatty acid synthase; *SCD1*, stearoyl-CoA desaturase-1; *CPT1*, carnitine palmitoyl-CoA transferase 1; *MRP2*, multidrug resistance-associated protein; *HFD*, high-fat diet; *NASH*, non-alcoholic steatohepatitis; *LDL-cholesterol*, low-density lipoprotein-cholesterol; *HDL-cholesterol*, high-density lipoprotein-cholesterol; *SOD*, superoxide dismutase; *GPx*, glutathione peroxidase; *GSH*, glutathione; *MDA*, malondialdehyde; *HCD*, high cholesterol diet; *VLDL*, very low-density lipoprotein; *G6PD*, glucose 6-P dehydrogenase

Based on multiple growing studies, melatonin has a role in the regulation of food intake and appetite (Fernández-Durán et al. 2007). Several pieces of evidence report the importance of melatonin in the regulation of food intake by researchers on different animals like pigs, mice, hamsters, and goldfish. The results obtained from this study are contradictory. In this regard, intracerebroventricularly injection of melatonin does not affect appetite and food intake. The intraperitoneal injection has significant effects and reduces this parameter (Pinillos et al. 2001). These inconsistent results depend on the spices studied and daily living habits; chronic melatonin administration positively induces mRNA levels of leptin. According to previous research, leptin can reduce appetite and food intake and stimulate the expression of POMC. After processing POMC to melanocortin peptide, the MC4R signaling pathway is activated by melanocortin and consequently decreases appetite. Neuropeptide Y, another factor that increases food intake, is decreased by leptin; hence, melatonin through leptin has a significant effect on appetite (Piccinetti et al. 2010; Volkoff et al. 2003).

Ghrelin, also known as the "hunger hormone," is produced by cholinergic cells in GIT and has an important

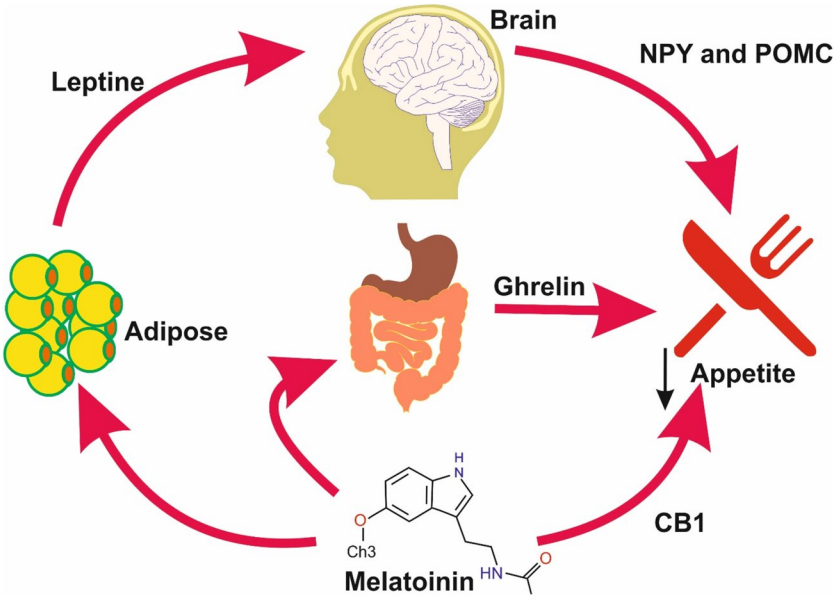

Fig. 4 The schematic diagram represents the crosstalk between melatonin and appetite

function in food intake and appetite. Ghrelin administration increases food intake and adiposity in mammalians. It seems that melatonin hurts ghrelin levels and chronic administration of melatonin reduces ghrelin levels and, subsequently, food intake; based on research, an orexigenic effect of ghrelin is applied by upregulation of neuropeptide Y. As a result, melatonin can repress the orexigenic effects of these two hormones (Miura et al. 2006; Mustonen et al. 2001). Moreover, melatonin has an orexigenic influence on CB1 and CB1-like protein levels. It can also lower CBI levels, which in turn causes a decrease in food intake. These actions of the endocannabinoid system also include the control of appetite and food intake (Piccinetti et al. 2010) (Fig. 4). Taken tougher, these results emphasized the central role of melatonin in controlling appetite and clearly show that melatonin is at the center of appetite signaling pathways; hence, this hypothesis can be posed that the administration of melatonin as the drug can control food intake and lead to weight loss obese people.

Conclusions

In response to food consumption, the enterochromaffin cells of the GIT produce and release more melatonin into the circulation than the pineal gland. Melatonin has a variety of positive effects on the GIT, ranging from the mouth cavity to the clone. Melatonin is an antioxidant that protects the oral cavity from periodontal disease and inhibits the growth and spread of oral cancer. Melatonin can prevent stress-induced stomach mucosal damage by inhibiting the release of gastric acid and pepsin, two essential invasive elements in the formation of gastric ulcers. With enhanced stomach blood flow, plasma gastrin levels, luminal NO release, and *H. pylori* eradication or a decrease in *H. pylori*-induced pro-inflammatory cytokine levels; melatonin also speeds up the healing of peptic ulcers. Because of its direct inhibitory effect on cell proliferation and metastasis, suppression of tumor cell invasiveness, activation of anti-oxidative stress, stimulation of the anticancer immune system, and induction of cancer cell apoptosis, melatonin is used as a complementary therapy in GIT malignancies in addition to chemotherapy and immunotherapy. The intestine, colon, and rectum tissues also have high levels of melatonin, which affects their permeability and movements. Melatonin affects intestinal food and minerals absorption directly and indirectly through increasing CCK release, pancreatic amylase, and mucosal bicarbonate, and the slowing movement of peristalsis. Furthermore, melatonin affects the intestinal bacterial composition; for example, it increases the beneficial bacteria such as lactobacillus in the intestine. Besides, melatonin is useful for reducing the symptoms of intestinal disorders such as IBS (by weakening serotonin function) and IBD (by reducing the severity of inflammation). Finally, melatonin is considered a regulatory hormone of food intake and appetite, and its administration can control food intake and lead to weight loss in obese people. Given these cases, melatonin can be considered a supplement with many benefits for the prevention and treatment of GIT disorders.

Abbreviations GIT: Gastrointestinal tract; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; TNF-α: Tissue necrosis factor-α; OLP: Oral lichen planus; LSD1: Lysine-specific demethylase; PDTX: Patient-derived tumor xenograft; CREBBP: CREB-binding protein; TIMP1: Metalloproteinase1; CXCL: CXC chemokine ligand; HPDLC: Human periodontal ligament cells; RANKL: Receptor activators of the NF-kB ligand; HGF: Human gingival fibroblast; CNS: Central nervous system; SOD: Superoxide dismutase; *H. pylori*: Helicobacter pylori

Author contributions The core of study came from MN-A and BY. All authors wrote the manuscript. Final editing was done by MN-A. BY and MN-A supervised the manuscript. The authors confirm that no paper mill and artificial intelligence was used.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate There is no involvement of humans or animals in this study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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