Review

The bacteriostatic property of melatonin targets peptic ulcer disease and cholangiocarcinoma

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ABSTRACT

The marked drop in the frequency of *Helicobacter pylori* infection resulting from the use of antibiotics and potent anti-acid medications has substantially lowered the prevalence of peptic ulcer disease in recent decades. Management of this condition, however, is challenging because of the escalating perils of antibiotic resistance and the abuse of anti-inflammatory drugs. For example, the increased prevalence of cholangiocarcinomas may associate with this peptic ulcer disease management including the prolonged use of proton pump inhibitors. Cholangiocarcinoma is one of the most lethal cancers and accounts for almost 15% of all hepatic malignancies. This review provides a concise summary of the latest findings in the pathogenetic mechanisms of cholangiocarcinoma, essentially focusing on peptic ulcer disease and its associated therapies. We also suggest interventions that may reduce *Helicobacter pylori* infection and peptic ulcers with the bacteriostatic agent, melatonin. Melatonin treatment may reduce the incidence of this devastating cancer or improve the outcome of individuals that develop this disease.

Key words: peptic ulcer disease, *Helicobacter pylori*, proton pump inhibitor, cholangiocarcinoma, melatonin.

1. INTRODUCTION

Peptic ulcer disease (PUD) encompasses both gastric and duodenal ulcers and is a massive threat to the health of global population due to its high morbidity (1). For years, surgical removal of gastric tissue has been a common treatment of PUD, but, often resulting in complications and high mortality rates. With the discovery of histamine H2-receptor antagonists (H2RAs) such as ranitidine and cimetidine in the early 70s, suppression of gastric acid secretion became a

conventional treatment for PUD. This treatment remarkably reduced the number of elective peptic ulcer surgeries (2).With the expansion of the use of the proton-pump inhibitors (PPIs), further improvement on both gastric and duodenal ulcer treatment was achieved (3).

A great deal has changed since the identification of *H. pylori* in the human gut. With the help of targeted antibiotics, new generations of H2RAs, and PPIs, great improvements in ulcer treatment have been achieved and this novel therapy significantly reduces the morbidity of patients. Despite a sharp decline in the total cases worldwide, one percent of Americans is still a victim of the dreaded PUD (4). Unfortunately, the use of H2RAs and PPIs is also accompanied by several side effects. These side effects are secondary to the acid-suppressive action of PPIs, which result in fundic gland polyps, hypergastrinemia, and enterochromaffin-like cell hyperplasia, thereby leading to carcinogenesis (5). Similarly, prolonged use of antibiotics is associated with increased drug resistance and may even exacerbate the existing ulcers (6). The acid-suppressive action of PPIs and bacterial resistance to antibiotics provide the optimal situation for another lethal condition, cholangiocarcinoma (CCA) (6, 7).

CCA is a group of heterogeneous malignant tumors that occur throughout the hepato-biliary tree. Currently, CCA accounts for ~15% of all hepatic malignancies and ~3% of gastrointestinal carcinomas and the incidence of CCA is constantly increasing globally (6). The difficulty to detect CCA combined with aggressive nature and resistance to chemotherapy render to the high mortality of CCA which account for ~2% of all cancer-related annual deaths globally. With an overall survival rate of 7-20%, the diagnosis, therapy, and awareness of CCA have not significantly improved recently (7).

Considering the potential role of peptic ulcer medications on the incidence of CCA, characterization of each of these drugs and their respective roles in the onset of CCA have become essential to understand the potential mechanisms involved in the pathogenesis. Herein, we summarize the current understanding of the role of conventional peptic ulcer medications on CCA, with emphasis on epigenetic aspects and molecular pathways. Also, we hypothesize that melatonin as a bacteriostatic agent will reduce the incidence of PUD, minimize the intermittent risk factors, and also substantially reduce the onset of CCA.

2. PEPTIC ULCER DISEASE

The term peptic ulcer is indicative of an injury to the digestive tract, resulting in mucosal breakage, stretching down to the level of the submucosa (8). Initially, a hyper-acidic environment combined with dietary and stress-mediated factors were considered to be the primary causes of most PUD. With the discovery of the involvement of *H. pylori* and unrestricted use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the latter half of the 20th century, this idea has been changed substantially (9).

2.1. Pathogenesis.

The breach in the gastric mucosal barrier due to elevated gastric acids followed by a noxious inflammatory reaction causes PUD. A variety of exogenous and endogenous stimuli promote ulcer formation by enhancing gastric acid production or diluting the mucosal bicarbonate layer. *H. pylori* and the overuse of NSAIDs are considered as two major risk factors of PUD (9).

Host reaction and the mucosal inflammatory response to *H. pylori* determine the outcome of the infection. The proteins including BabA and OpiA synthesized by *H. pylori* facilitate the

attachment of bacteria to the gastric epithelium, thus, contributing to the virulence and the host immune response from *H. pylori*. In addition, these organisms also release urease, creating an alkaline milieu that enables the bacterium to successfully evade the highly acidic environment in the stomach (10, 11).

As to NSAID, the risk of PUD-associated complications is four times high in NSAID users compared to non-users (12). Thus, NSAIDs are ranked as the second most important causative factor responsible for the onset and progression of the disease. Initially, it was thought that topical injury and reduction of mucus bicarbonate caused by NSAID were the main mechanisms related to gastric damage (13). Subsequently, it was identified that the damages were induced by the suppressed gastric prostaglandin synthesis by NSAID (14).

2.2. Epidemiology.

Epidemiologically, the lifetime prevalence of PUD in the global population is approximately 5−10% with an incidence of about 0·1–0·3% per year (15). Central America, South America, Europe, and Asia, have seen a rapid decline in mortality from gastric and duodenal ulcers irrespective of the differences in healthcare systems and socioeconomic statuses (16). This drop is associated with a reduction in *H. pylori*-associated PUD.

Although the increased use of NSAIDs does not seem to justify the recent trends in ulcer-related mortality, numerous studies have reported decreasing hospital admissions for complications of PUD in the 21st century. With an incidence of 79 cases per 100,000 people per year and annually less than 30 cases of PUD complications (16–18), these figures possibly indicate the success of the current therapeutics on this disease (18). However, there have been several instances where severe complications have surfaced due to the prolonged use of such PUD-targeted medications.

2.3. Management and therapeutics.

Research on the pathogenesis and treatment of PUD has made remarkable progress, which will hopefully help to revolutionize the medical approach to ulcer management. Since Schwarz's percept of "no acid, no ulcer", the quest for a suitable management strategy for PUD has been directed at this goal, i.e., to reduce gastric acid secretion and enhance the mucosal defense (19). Currently, the objectives of anti-ulcer therapies are more precise and target-oriented. These include pain reduction, ulcerative wound healing, averting complications, and preventing a possible relapse. Thus, limiting ulcer recurrence is of utmost importance for achieving the long-term goal of reducing global morbidity and mortality (20). The current management protocols for PUD, along with the doses and side effects of different drugs used, are summarized in Table 1.

2.3.1. *H. pylori*-associated ulcers.

A variety of studies have suggested that the eradication of *H. pylori* infection itself is sufficient to heal gastroduodenal ulcers and is also sufficient to prevent relapse and intermittent bleeding in the absence of remedial acid-suppressive therapy (20). However, this successful treatment of *H. pylori* infection currently faces a global challenge because of the increased resistance of bacteria to antibiotics. Currently, the first-line regime consists of a PPI and two antibiotics (clarithromycin and amoxicillin), for consecutive 7−14 day use (23–26). In many

developed countries, due to increasing cases of antibiotic resistance, the effectiveness of this combined regimen for *H. pylori* infection fell from 90% to less than 70% (25, 26). Thus, any treatment should take into consideration the outcomes tested for antimicrobial susceptibility (25). Unfortunately, such tests are not commonly available in countries with low socioeconomic status and rapidly expanding populations. Accordingly, the first-line therapies should be individualized, keeping in mind the local prevalence of antibiotic resistance if it can possibly be determined. For instance, when the bacterial susceptibility test is not available, PPI-based triple therapy regimens have been modified to not include clarithromycin in areas with a local clarithromycin resistance rate higher than 15% (26, 27). As a result, this leads to an increased dependence on PPIs and H^+ channel blockers to combat ulceration. Seemingly, using higher doses of PPI (twice the conventional dosage) and changing the duration of the therapy from 7 days to a maximum of 14 days may aid in the eradication of *H. pylori* (9).

2.3.2. NSAID-associated ulcers.

The overuse of NSAIDs is the most significant cause of PUD in nations with a declining prevalence of *H. pylori* infections. In such situations, if patients discontinue the use of NSAID, the ulcer healing would be improved. However, for certain patients who are required to continuously use NSAIDs because of some underlying infirmity, this would delay the overall healing process of the ulcer. There are some strategies available for restricting the onset of gastroduodenal ulcers and arresting their progression, thus, enabling patients to use NSAIDs. These include the combined use of NSAIDs with PPIs, H^+ receptor antagonists, or misoprostol (28). Substitution of non-selective NSAIDs with COX-2-selective NSAIDs is another strategy. For example, a combination of a COX-2-selective NSAID with a gastroprotective agent can prove to be a viable option to address this issue (29,30).

The increasing prevalence of *H. pylori*-resistance with the recurrence of idiopathic ulcers is frequently associated with bleeding complications and death (31). Although long-term PPI treatment is regularly recommended, whether this strategy improves clinical outcomes of PUD is yet to be confirmed.

3. THE POTENTIAL ASSOCIATION OF PUD AND LONG TERM PPI USE ON THE HEPATOBILIARY MALIGNANCIES

Hepatobiliary cancer continues to be one of the cancers with high mortality rates (28). PUD caused by *H. pylori* infection has emerged as the leading cause of such malignancies by stimulating inflammation and consequential neoplastic progression (32). The eradication of *H. pylori* can substantially diminish the incidence of such carcinomas. In contrast, the unrestricted use of pain medications and growing resistance of *H. pylori* to conventional antibiotics may promote PUD and its associated malignancies.

PPIs are a class of medications, which are indispensable for the treatment of PUDs and have been widely used in both developed and developing countries (33). However, their intense gastric-acid suppressive activity has raised concerns about their association with carcinogenesis (34). These concerns are due to the fact that PPIs can induce hypergastrinemia and bacterial overgrowth in the gut (35). One of the most prevalent carcinomas triggered by PUD and its related therapeutics is CCA.

Table 1: A tabulation of the drugs available for PUD treatment.

Function	Classification	Name of Drug	Recommended Doses	Side Effects
Gastric acid suppression	Proton pump inhibitors	Omeprazole	20mg/day; 40mg/day for faster healing	Nausea, dizziness, headache, diarrhea, abdominal pain, muscle, and joint pain, leucopenia, hepatic dysfunction, atrophic gastritis (20)
		Esomeprazole	20-40mg/day	
		Lansoprazole	15-30mg/day for ulcer healing	
		Pantoprazole	40-120mg/day	
		Rabeprazole	40-80mg/day	
		Dexrabeprazole	10-20mg/day	
	H_2 antihistamines	Ranitidine	300mg/day ulcer healing; 150mg for maintenance	Headache, diarrhea/constipation, dizziness, bowel upset, rare disorientation, rash, transient elevation in plasma aminotransferases; high doses for long periods can lead to loss of libido, gynecomastia, impotency, decreased sperm count (20)
		Famotidine	40mg/day for ulcer healing; 20mg for maintenance	
		Roxatidine	150mg/day for ulcer healing; 75mg for maintenance	
		Cimetidine	800mg for ulcer healing; 400mg for maintenance ;	
	Anticholinergics	Oxyphenonium	5-10mg/day	Dry mouth, constipation, urinary retention (21)
		Propantheline	15mg/day	
		Pirenzepine	100-150mg/day	
	Prostaglandin analog	Misoprostol	800µg/day	Diarrhea, abdominal cramps, uterine bleeding, abortion (20)
Anti-*H. pylori* drugs	N/A	Clarithromycin	1g/day	Diarrhoea, nausea, taste distortion, stomatitis, bloating (22)
		Amoxicillin	2g/day	
		Tinidazole	1g/day	
		Tetracycline	1-2g/day	
		Metronidazole	1-2g/day	
Antacids	Systemic	Sodium citrate	1g neutralizes 10mEq HCl	Alkalosis, some of them may produce CO_2 in the stomach causing distention, discomfort, acid rebound, may worsen edema and CH, increases Na^+ load (20)
		Sodium bicarbonate	1g neutralizes 12mEq HCl	
	Non-systemic	Magnesium hydroxide	1g neutralizes 30mEq HCl	
		Aluminium hydroxide gel	1g neutralizes 1-2.5mEq HCl	
		Magnesium trisilicate	1g neutralizes 1mEq HCl	
		Magaldrate	1g neutralizes 28mEq HCl	
		Calcium carbonate	1g neutralizes 20mEq HCl	
Ulcer protective	N/A	Sucralfate	4g/day	Constipation, hypophosphatemia, dry mouth, nausea, diarrhea, headache, dizziness (20)
		Colloidal bismuth sulphate	480mg/day	

4. CCA

CCA is a group of heterogeneous epithelial tumors that form within the biliary tree. As per prevalence, CCA holds the second position among primary hepatic malignancies, accounting for approximately 15–20% of the newly diagnosed cases (28). Based on their location, there are three subtypes of CCA **(Table 2)**: intra-hepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA) (36). Surgical intervention has always been the first choice for CCA, irrespective of its subtype. However, only a small portion of the patients who are in the early stage of the disease are considered eligible for surgery, with iCCA having the highest (63%) and dCCA having the lowest (23%) 5-year survival rate (37).

In majority of the cases, CCA is generated by malignant transformation of cholangiocytes, but there are some instances where transformed epithelial cells within peribiliary glands or biliary stem cells also trigger the onset of CCAs. Multiple studies suggest that subsets of CCA and mixed hepatocellular carcinoma/CCA also originate from hepatic stem/progenitor cells (38).

Table 2: Classification of CCA

Type	Occurrence	Subtype	Symptoms
Intrahepatic CCA	Intrahepatic biliary tract (39)	Mass-forming (40)	Cachexia, abdominal pain, night sweats, fatigue (40)
		Periductal-infiltrating (40)	
		Intraductal (41)	
		Undefined (41)	
Perihilar CCA	Between second-order biliary ducts up to the site of cystic duct origin (39)	Periductal (39)	Painless jaundice, cholangitis, malaise, abdominal discomfort, nausea, anorexia (41, 42)
		Intraductal (39)	
Distal CCA	Between cystic duct and ampulla of Vater (39)	Well to moderately differentiated adenocarcinoma (39)	Painless jaundice (39)

4.1. Risk factors.

Numerous risk factors contribute to the onset of CCA. These include parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis, and toxins (43). A clear association between PUDs and CCAs has been observed (44), especially, when this PUD is caused by *H. Pylori* infection (45). Thus it is hypothesized that *H. pylori* may play a key role in carcinogenesis by increasing the kinetics of the biliary epithelial division (46). However, the mechanisms driving the generation of CCA induced by PUD are complex and not well defined.

4.2. Pathogenesis.

CCA typically develops on a background of inflammation (44). There are a plethora of processes known to cause inflammation in the gut and the hepatobiliary tree. The focus of this

article is solely given to the role of PUD. Here, two scenarios on the chronic development of peptic ulcers that will trigger and accelerate the onset of CCA are proposed. A detailed overview of these has been illustrated in Figure 1.

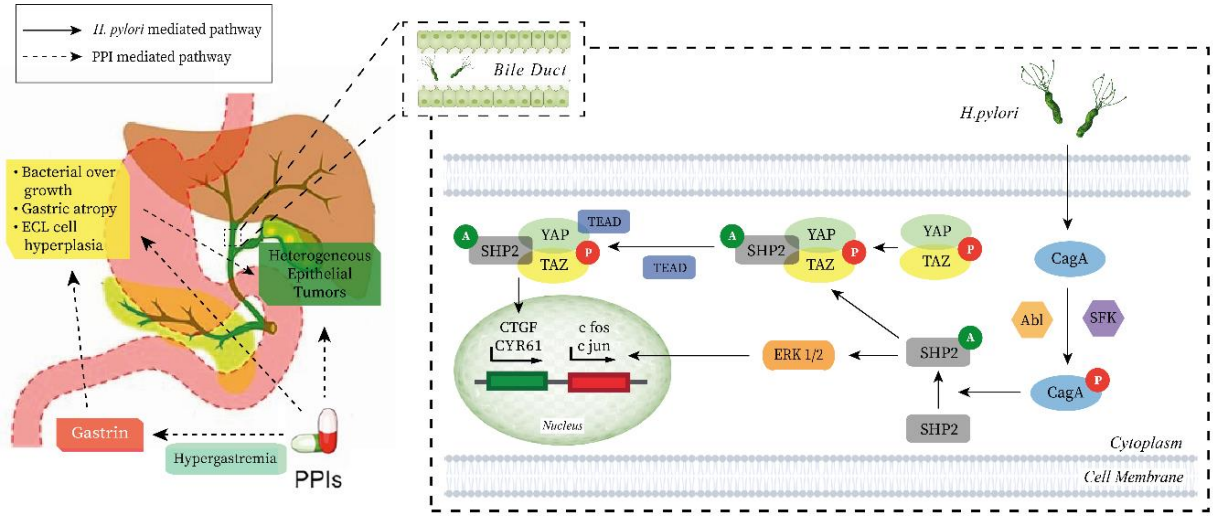

Fig. 1: The potential mechanisms associated with the genesis of CCA caused by *H. pylori* infection and prolonged PPI administration.

H. pylori exhibits its oncogenic properties via the CagA (Cytotoxin-associated gene A) pathogenicity island, in which CagA is phosphorylated through Abl and SFK (Src family kinase). Phosphorylated CagA activates SHP2 (Src homology region 2 (SH2) - containing protein tyrosine phosphatase 2) which further activates ERK 1/2 (Extracellular-signal-regulated kinase) to promote the downstream transcription of c fos and c jun. Also, YAP (Transportation analysis zone) and TAZ (Transportation analysis zone) dimerize and get activated in the presence of SHP2. This multimeric complex fuses with TEAD (TEA domain transcription factor) and translocated inside the nucleus and ultimately activates downstream transcription of CTGF (Connective tissue growth factor) and CYR61 (Cysteine-rich angiogenic protein 61). Prolonged use of PPI at the same time induces hypergastrinemia which promotes the formation of multiple heterogeneous epithelial tumors. This results in uncontrolled cell growth and loss of contact inhibition in the hepatobiliary epithelial cells.

4.2.1. Role of *H. pylori.*

The *H. pylori* colonies located in antral portions of the stomach which can stimulate gastric secretion are the hallmark of PUD-associated CCA (47). The presence of *H. pylori* colonies in the hepatobiliary tree, especially in patients with severe infections has also been reported (48). With the successful characterization of different *Helicobacter* strains in the biliary system, their roles in triggering malignant biliary diseases have been defined (48). Based on the current findings, the inflammation followed by epithelial cell proliferation and interference with the cell cycle via modifications in signal transduction seems to be the most plausible explanation of carcinogenesis. However, there have been speculations that the *H. pylori* virulence factor CagA *(Cytotoxin-associated gene A)* may mediate carcinogenesis in the hepatobiliary tree (6). It seems

that CagA, an oncoprotein, interferes with signal transduction pathways (49–53) and the host's response to *H. pylori* antigens via the formation of cytokines and other inflammatory mediators (54–56).

4.2.2. Role of PPIs.

PPIs are the first choice for treating PUD, because of their safety and efficacy (33, 57). Since their initial use in the 1980s, PPIs have become the most widely prescribed medications (58). The long-term use of PPIs has also become a crucial issue concerning their toxicity (59). Their potent acid-suppressive effect has long been suspected as a risk factor for neoplasia, along with other serious disorders related to nutrition, bone metabolism, and infections (59, 60). Gastrin peptides, along with their dedicated receptors, potentiate the progression of gastrointestinal malignancies in the presence of inflammation (44). Hypergastrinemia is considered to be the major mechanism associated with PPI-induced carcinogenesis. It causes a persistent elevation in gastric antral pH and spurs cell proliferation leading to carcinogenesis and tumor growth (35). Recent studies have demonstrated that PPI use is associated with peri-ampullary tumors (61). Peng *et al*. have reported that the odds of onset of CCA are positively related to PPI use (7). Hence, it is reasonable to consider that PPI use and CCA are intercorrelated (7,62,63).

5. POTENTIAL EFFECTS OF MELATONIN ON PUD AND ITS ASSOCIATED CCA

Based on the literature, the number of studies to search for new treatments on PUD has continuously increased throughout the years. However, interventions that simultaneously deal with both PUD and CCA are scarce. The majority of the current research focus on minor modifications to the conventional triple therapy regime and few attempts are made to develop alternative interventions (64). Here, we propose a potentially important therapy for PUD/CCA with melatonin. Melatonin is a well-known sleep modulator with actions on circadian rhythms (65). In addition, melatonin also plays an active role in numerous other biological activities including its antioxidant and anti-inflammatory actions (66, 67). It also has profound effects on the gastrointestinal tract. It promotes gastric motility, nutrient absorption, and food digestion. The melatonin is synthesized and secreted from the gastrointestinal mucosa which, provides onsite protection against noxious internal and external insults and maintains gastrointestinal integrity. For example, under the condition of PUD, melatonin promotes the activity of antioxidant enzymes, gastric blood flow, and mucous secretion while reducing acid secretion, and interferes with the prostaglandin-dependent pathways to accelerate ulcer healing and prevent its recurrence (68–71). Another mechanism suggests that melatonin can suppress the activities of metalloproteinases 3 and 9, which cause serious implications on PUD and CCA. These activities are probably mediated by melatonin receptors since luzindole (melatonin receptor antagonist) significantly attenuates the ulcer healing effects of melatonin (72, 73). The accumulated evidence shows that melatonin can reduce the incidence of PUD (71) as well as CCA (74, 75).

5.1. Bacteriostatic effects of melatonin.

Sufficient evidence has proved the cause-and-effect association between *H. pylori* infection and gastric ulcers. Controlling the infection will reduce the onset of PUD. As a result, antibiotics including clarithromycin and amoxicillin serve as the first choice for treating *H. pylori*-induced

infections in the gut (64). However, frequent use of these drugs has caused a surge in antibiotic resistance (76).

On the other hand, melatonin supplementation exhibits a profound protective effect on *H. pylori*-induced chronic gastric ulcers, dyspepsia, and accelerates their healing processes (69, 77). This effect may relate to a potential bacteriostatic activity of melatonin on *H. pylori.* Tekbas and colleagues (78) have tested the role of melatonin against both gram-positive and gram-negative bacteria. The results showed a higher inhibitory potential of melatonin on gram-negative bacteria than that in gram-positive ones (78). The reason may be related to the protein glycopeptide and lipopolysaccharide-rich cell envelope of the gram-negative bacteria. Melatonin limits the uptake of linoleic acid and total fatty acids, which serve as an essential component for the formation of the cell envelope in gram-negative bacteria (79, 80). Hence, *H. pylori,* being gram-negative, can be inhibited by melatonin. Konar *et al.* reported that melatonin, at the concentration of 1000 µg/ml, significantly reduced the lipid level of *Saccharomyces cerevisiae*. While at 300 µg/ml, it significantly reduced lipid levels of *Candida albicans* (81). All these pieces of evidence suggest the potential action of melatonin in controlling *H. pylori* infection.

Additionally, melatonin has a high metal binding capacity (82). This enables melatonin to bind to Fe^{2+} with great potency. Hence, it considerably inhibits bacterial division as Fe^{2+} is essential for the replication of the bacteria. This prolongs the lag phase of bacterial replication and, in some cases, might even substantially restrict bacterial growth (78).

5.2. Altered melatonergic system and its components in CCA: AANAT (aralkylamine N-acetyltransferase), melatonin, and its receptors.

Melatonin levels in bile are 2 to 3 times higher than that in day-time serum levels (83). The immense high level of melatonin in bile is essential for preventing the biliary and intestinal epithelium damages elicited by bile acids and oxidized cholesterol derivatives, as well as inhibiting PUD and its associated malignancy (83). It has been reported that melatonin prevents biliary hyperplasia and provides a chemopreventive effect in CCA treatment by attenuating oxidative damage (74). *H. pylori* infection-induced PUD is associated with lowered melatonin levels and decreased expression of *AANAT* in the gastric mucosa (77, 84). Dysregulation of AANAT/melatonin and melatonin receptor axis is observed in CCA and decreased secretion of melatonin enhances CCA growth (74). Han *et al.* hypothesized that higher levels of melatonin are associated with reduced chances for the development of CCA (74). This can be achieved by upregulation of the expression of *AANAT* (one of the key regulatory enzymes of melatonin biosynthesis). Melatonin may retard tumor growth due to the presence of melatonin receptors on these tumors. Han and his colleagues identified an autocrine loop between AANAT and MT receptors. Treatment with melatonin increased the sensitivity of the MT receptors, which in turn resulted in the upregulation of *AANAT* expression (74, 85) and an accumulation of melatonin in the hepatobiliary tree. Melatonin in elevated levels inhibits the carcinogenic growth of the bile duct epithelium via the mitochondrial apoptotic pathway as shown for other cancers (86). The high levels of melatonin may also contribute to its bacteriostatic abilities.

6. FUTURE PERSPECTIVES AND CONCLUSION

This review provides insights into the potential association between melatonin and PUD. Additionally, this review also focuses on the likelihood of PUD-induced CCA. CCA, in general,

has a high mortality rate often due to its delayed detection. Based on the mechanisms mentioned above, melatonin is recommended to be used to combat PUD/CCA in addition to its low cost and safety. Melatonin, also shares structural similarities with omeprazole, thus making it a more suitable candidate replacing conventional PPIs in treating PUDs. Because of the severe side effects, several hospitals in the United States have already issued an order to stop the use of all PPIs (87) thus, compelling clinicians to conduct more studies on melatonin against PUD and CCA. The reduced use of PPIs may lead to fewer cases of CCA.

Here, we address that the bacteriostatic effect of melatonin may be the major mechanism of melatonin to reduce PUD and its associated CCA. The melatonergic system including AANAT, melatonin receptors, and high-level melatonin levels in the gut and hepatobiliary tissues facilitates an endogenous autocrine loop of melatonin's action. Further experiments are necessary to identify the value of melatonin as a possible treatment for these serious gastrointestinal problems. Considering the limitations of current therapies, a new effective treatment paradigm including melatonin is likely to be widely accepted and is certainly needed.

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AUTHOR'S CONTRIBUTION

Dr. AC and Dr. DB contributed to the conception, critically corrected and approved the manuscript. RM prepared, drafted, and edited the manuscript, tables, and figures. MD contributed to preparing the tables and editing the manuscript. SS helped in editing the manuscript. We are deeply indebted to Dr. DunXian Tan for his critical reading and meticulous editing of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AANAT:	Arylalkylamine N-acetyltransferase
BabA:	Blood group antigen binding adhesin
CagA:	Cytotoxin-associated gene A
CCA:	Cholangiocarcinoma
COX-2:	Cyclooxygenase-2
dCCA:	Distal cholangiocarcinoma
H. pylori:	*Helicobacter pylori*
H2RA:	Histamine H2 - receptor
iCCA:	Intra-hepatic cholangiocarcinoma
NSAID:	Non-Steroidal Anti-inflammatory Drug

OpiA: Outside pathogenicity island A
pCCA: Perihilarcholangiocarcinoma
PPI: Proton pump inhibitor
PUD: Peptic ulcer disease
SFK: Src family kinase
SHP2: Src homology region 2 (SH2) - containing protein tyrosine phosphatase 2
TAZ: Transportation analysis zone
YAP: Yes-associated protein
ERK: Extracellular-signal-regulated kinase
TEAD: TEA domain transcription factor
CTGF: Connective tissue growth factor
CYR61: Cysteine-rich angiogenic protein 61

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