Review

Melatonin promotes gastric healing by modulating the components of matrix metalloproteinase signaling pathway: a novel scenario for gastric ulcer management

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ABSTRACT

Over the past few decades, since the induction of antibiotics and proton pump inhibitors (PPI) as a therapeutic tool in controlling gastropathy, a substantial decline in the incidence of gastric ulcer and its related manifestations has been achieved globally. However, there are a lot of skeptics on the steady rise in the list of complications following long-term use of these drugs, especially in chronic and elderly patients. Hence, the search for a sustainable cure for these gastropathies has never actually ended; this let us consider that melatonin, an endogenous antioxidant, might have a utility in this respect. Although researchers have linked melatonin with accelerated post ulcerative wound healing, many of these studies have failed to identify the confounding factors and plausible healing mechanisms. In this review, we attempt to identify the underline mechanisms as to the protective effects of melatonin on a variety of gastropathies. Based on the evidence, we select the matrix metalloproteinases (MMPs) to be the main targets of melatonin. MMPs play a key role in maintaining the balance between extracellular matrix degradation and tissue remodeling, therefore, they act as the integral connection between the ulcer manifestation and healing. Thus, gastric ulceration occurs where this balance is disrupted. Melatonin can preserve this balance during the onset of gastric ulcers. In this review, we have also discussed the effects of melatonin on the different isoforms of MMPs and their roles in gastric ulceration, respectively. We hope that this will bestow us with a better understanding of the development of the gastric ulcer, as well as its cure.

Key words: Melatonin, gastric ulcer, matrix metalloproteinase, *Helicobacter pylori*, non-steroidal anti-inflammatory drugs (NSAID), oxidative stress, antioxidant.

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1. INTRODUCTION

Gastric ulcers, despite its declining incidence, hold an estimated lifetime prevalence of 5-10% among the global population (1). This disorder is associated with an annual fatality toll exceeding 6,000 and is accompanied by the hospitalization of over a million per year in the

United States of America only (2). The number implies a major threat to the world's population due to its high morbidity and mortality rates (3). Based on the pathogenesis, gastric ulcer can be considered as an outcome of a disrupted equilibrium between the defensive (mucosal blood flow, prostaglandins, mucus-bicarbonate layer, cellular regeneration) and offensive factors (hydrochloric acid, pepsin, bile salts) (4, 5). Precisely, the pathologies of this disorder can be broadly categorized into three sub-groups, namely, *H. pylori*-positive, *H. pylori*-negative-non-NSAID and NSAID associated gastric ulcers. Although the triple therapy regime is the most widely accepted treatment for gastric ulcers (3), they are also associated with multiple adverse manifestations which prevent some patients from seeking this treatment.

MMPs or matrixins are a family of structurally related, highly homologous Zn^{2+} containing endopeptidases (6). They precisely regulate the degradation of the extracellular matrix (ECM). This process is necessary for normal physiological remodeling that includes morphogenesis, development and tissue repair (7). It is estimated, at least, 24 members of MMPs are present in humans, rodents and amphibians (8). Initially, these Zn- dependent proteases were known to degrade numerous structural components of the ECM while, currently, their specific proteolytic targets have been extensively expanded to substrates including an array of other proteinases, clotting factors, proteinase inhibitors, latent growth factors, chemotactic molecules, cell surface receptors, growth factor binding proteins, and cell-cell and cell-matrix adhesion molecules (9).

The strong association between MMPs and gastric ulcers let researchers reconsider their intricate role in ulcer development and healing (10–12). For instance, MMP-9 is related to the initiation of gastric ulceration while MMP-2 is involved in the remodeling of the gastric ECM (12, 13). The regulation of expression of MMP-9 and -2 are complementary in both acute and chronic gastric ulcerations (11, 13).

Numerous antioxidants also exhibit beneficial effects on gastric ulcers by inhibiting lipid peroxidation and other free radical-mediated processes, (11, 12). However, we speculate that some of these effects of antioxidants may be mediated by MMPs. Preliminary data indicate that melatonin can act on MMPs. Melatonin, a natural antioxidant, not only regulates the circadian rhythm of mammals (14) but also maintains the redox status of the cell (15). Apart from the pineal origin, melatonin is also synthesized in several other organs and tissues (16) especially, the gastric mucosa has recorded a much higher secretion rate of melatonin than that in the pineal gland (17). The antioxidant activity of melatonin has been well documented to protect cells and tissues from ROS damage (18–20).

In this review, we focus on the role of MMPs in-synchrony with ROS in the development of gastric ulcers and thus, attempt to identify a cross-talk between melatonin and MMPs as to their beneficial effects on gastric ulcer. We hope that this discussion will provide some new thoughts for researchers to target this disorder.

2. PATHOGENESIS OF GASTRIC ULCER

2.1. *Helicobacter pylori.*

Ever since Barry Marshall and Robin Warren first successfully isolated *Helicobacter pylori* from the human stomach, its role in gastric ulcers has been extensively studied (21). It has also been classified as a class I carcinogen by WHO. The prevalence of humans infected with *H. pylori* have been recorded worldwide and it varies widely in countries and populations (22). *H. pylori*-positive patients have an estimated 10-20% lifetime risk of developing gastric ulcers (23). About 85% of gastric ulcer occurrence is associated with *H. pylori* infection. The organism's ability to interact intimately with the gastric epithelium is a

hallmark in *H. pylori* pathogenesis (24) and its motility remains uninterrupted even in the highly viscous mucus layer, where it resides. *H. pylori*-induced ulcer in human greatly depends upon the localization of the infection (25). Chronic inflammation induced by *H. pylori* leads to the eventual disruption of normal gastric mucosal architecture and the destruction of gastric glands (26). In a corpus predominant phenotype of this infection, hypochlorhydria occurs with the suppression of proton pump by *H. pylori* and the activity of cytokines produced by the infiltrated immune cells (27). Interestingly, a remarkable enhancement of IL-1β production caused by *H. pylori* infection potentially inhibits gastric acid secretion (28) and platelet-activating factor, is also a potent ulcerogen (29). *H. pylori*, with the help of a proton gated inner membrane channel, facilitate diffusion of urea from the gastric lumen into itself where the cytoplasmic urease converts the urea into ammonia and carbon dioxide. The ammonia diffuses into the periplasmic space and creates a higher pH microenvironment for the bacterium that makes its survival possible in an extremely acidic environment. This survival strategy is particularly important for its direct inhibition of acid secretion from the parietal cell (30). *H. pylori* separate the luminal and the serosal side of the gastric epithelium (31), thereby allowing itself to interact with the parietal cell membrane receptors (32). Thereafter the bacterium mobilizes cell proteins that inhibit acid secretion. It secretes virulence factors that perturb the synthesis of the ATP4A subunit of the proton pump and impairs acid secretion from the parietal cells thereby leading to gastric atrophy which ultimately leads to ulceration in due course (32). Although numerous broad-spectrum antibiotics are being used for diminishing the prevalence of *H. pylori* in patients, they are also associated with a number of serious implications which compel the medical practitioners to withdraw the usage of the drug in chronic patients (33).

2.2. Non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs are nowadays one of the most common medicines prescribed for pain and inflammation around the world. It has been reported that 111 million prescriptions were written for NSAIDs in the year 2000 for the USA (34). With a reduced incidence of *H. pylori* infection, NSAIDs have emerged as the leading cause of gastrointestinal injury (35). The chemical classification of NSAIDs include indoles, p-aminophenols, aryl propionic acids, enolic acids, salicylates, and heteroaryl acetic acids. However, this classification is not sufficient to distinguish these drugs according to their most important functions (36). Traditionally, NSAIDs are said to act by inhibiting the enzymes involved in prostaglandin synthesis (37). Nevertheless, there is irrefutable evidence suggesting that inhibition of cyclooxygenases（COX）is, not the sole mechanism of NSAID to induce gastric ulcer. The discovery of two different, COX-1 and COX-2 led to a new classification of NSAIDs based on their selectivity towards different COX isoforms. Thus NSAIDs can be classified into non-selective COX inhibitors, preferential COX-2 inhibitors, selective COX-2 inhibitors and analgesic-antipyretics (Table 1) (38). NSAIDs have both local and systemic effects on gastric tissue. The local injury is initiated by the initial erosion of the mucosal layer and disruption of the gastric epithelial cell barrier. In addition, NSAID induced ulcer development mainly via their systemic effect usually occurs in two ways. It can occur either in a prostaglandin-dependent pathway by COX-1 and COX-2 inhibition or, in a prostaglandin-independent pathway through inhibition of H_2S, NO and polyamines. COX-inhibition depletes mucosal prostaglandins and this leads to the activation of other mediators of gastric mucosal defense to elicit the reparative responses. Development of ulcers occurs when these compensatory mechanisms are overreacted. COX-1 is essential for housekeeping in the gastric mucosa (39). On the other hand, COX-2 up-regulation is involved with inflammation (40). A sharp decline in the levels of prostaglandin is a well-established concomitant event in a typical instance of

COX-1 inhibition. The decrease in prostaglandin level causes gastric hypermotility with consequent micro-vascular disturbances, reduced mucosal blood flow and vascular injury. This results in neutrophil activation and proceeds to cause gastric damage that ultimately advances to ulceration (41). Interestingly, several recent studies have demonstrated that both COX-1 and COX-2 inhibition is essential for inducing gastric injury which suggests that there might be a housekeeping role for COX-2 along with COX-1, in the stomach (42). Currently, PPIs are considered to be the most effective therapy for full spectrum recovery of drug-induced gastric injury. However, their potent acid-suppressive action is known to induce several structural and functional changes within the gastric mucosa, including, enterochromaffin-like cell hyperplasia, fundic gland polyps and hypergastrinemia, which might even be exaggerated in the presence of a typical *H. pylori* infection (43).

Table 1: Classification of NSAIDs.

Classification	Chemical Nature	Drug
Non-Selective COX inhibitors (traditional NSAIDs)	Salicylate	Aspirin
	Propionic acid derivatives	Ibuprofen Naproxen Ketoprofen Flurbiprofen
	Anthranilic acid derivative	Mefenamic acid
	Aryl-acetic acid derivative	Diclofenac Aceclofenac
	Oxicam derivative	Piroxicam Tenoxicam
	Pyrrolo-pyrrole derivative	Ketorolac
	Indole derivative	Indomethacin
	Pyrazolone derivative	Phenylbutazone Oxyphenbutazone
Preferential COX-2 inhibitors	Aromatic ether derivative	Nimesulide
	Oxicam derivative	Meloxicam
	Methyl ketone derivative	Nabumetone
Selective COX-2 inhibitors	Pyrazole derivative	Celecoxib
	Bipyridine derivative	Etoricoxib
	Sulfonamide derivative	Parecoxib
Analgesic-antipyretics	Paraaminophenol derivative	Paracetamol
	Pyrazolone derivative	Metamizole
		Propiphenazone
	Benzoxazocine derivative	Nefopam

3. MATRIX METALLOPROTEINASES

MMPs are a family of Zn^{2+} and Ca^{2+} dependent endopeptidases capable of degrading the ECM at neutral pH. Based on recent findings the twenty-four members of the MMP family include interstitial collagenases, stromelysins, gelatinases, matrilysin, enamelysin, metalloelastase, membrane-type MMPs and other MMPs (44). They are generally synthesized as transmembrane or secreted pro-enzymes which are subsequently cleaved at

their amino-terminal to obtain the activated form. It is suggested that a cysteine (Cys) residue ligated with the Zn moiety at the active site is responsible for keeping the enzyme at its latent state. Likewise, the dormancy of the pro-enzyme is interrupted when the cysteine switch mechanism is triggered due to the disruption of this Zn-Cys interaction (45). As a family, MMPs are known to degrade most components of the ECM. They are activated or inhibited by several chaotropic agents (44) and anti-inflammatory medicines (46) which we shall discuss elaborately in this article.

3.1. Role of MMPs in ECM degradation, inflammation and pro-ulcerative effects.

Recently, the potential effects of MMP in gastric ulcers have drawn great attention from researchers. MMPs play a central role in the timely breakdown of ECM for tissue remodeling (47). Studies show that expressions of MMP 1, 3, 7, 9 and 10 are significantly upregulated when the gastric tissues are exposed to several conventional and non-conventional ulcerogens (48, 49). The increased expression of MMPs has also been observed in many inflammatory diseases (6). However, not all isoforms of MMP are overexpressed in an ulcerogenic environment. The downregulations are observed for MMP 2 and 14 (50). The differentiated expression patterns of the MMP isoforms indicate a distinct regulatory mechanism for each isozyme (51). This has led to a plethora of hypotheses summating to an exceedingly interlinked pathway with numerous transcript and growth factors (48) (Figure 1).

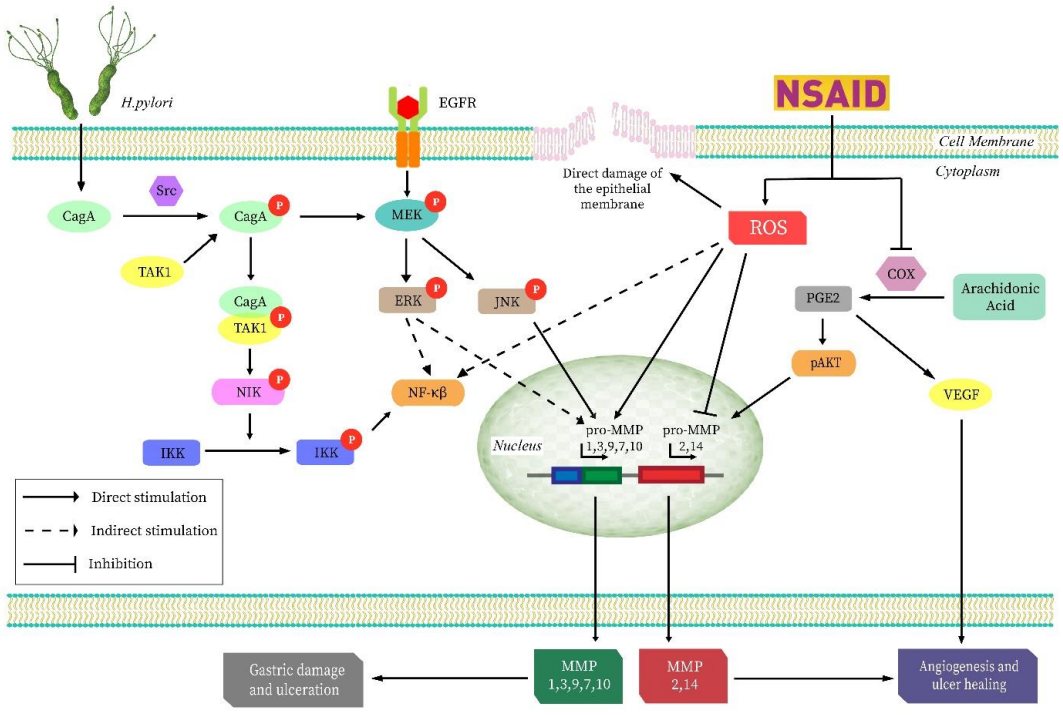

Fig.1: *H. pylori* and NSAID mediated gastric ulceration through the MMP pathway.

CagA: Cytotoxin-associated gene A, TAK1: Transforming growth factor-β-activated kinase 1, NIK: NF-κβ -inducing kinase, IKK, NF-κβ: Nuclear factor-kappa B, MEK: Mitogen-activated protein kinase kinase, ERK: Extracellular-signal-regulated kinase, JNK: c-Jun N-terminal kinase, COX: Cyclooxygenase, PGE2: Prostaglandin E2, VEGF: Vascular endothelial growth factor.

3.2. *H. pylori*: cagA dependent MMP expression in gastric ulcers.

Colonization of *H. pylori* in the gastric lining is one of the major factors responsible for the incidence of gastric ulcer in humans. However, the majority of signaling pathways dictating the inception of ulcers yet remains to be unveiled. Concerning recent literature, MMPs play an integral role in the onset of *H. pylori*-induced ulcers and also modulate the wound healing process via ECM degradation. For example, a specific strain of *H. pylori* is known to house an oncogenic gene called *cagA* (52–54). Its activation translates to an immune-dominant antigen which associates with numerous pathological alterations in the gut (54). The *cagA* gene product, upon entering the gastric epithelial cells via bacterial type IV secretion, interacts with numerous host proteins via an intrinsically disordered tail, containing the EPIYA and the CagA multimerization motifs (55, 56). An Src like tyrosine kinase initiates the signaling cascade by phosphorylating the CagA protein at its EPIYA domain (55). The phosphorylated CagA protein then physically associates with another host protein called transforming growth factor-β-activated kinase 1 (TAK1) (57) which in turn activates NF-κβ -inducing kinase (NIK). NIK relays its signal downstream by phosphorylating IκB kinases (IKKs), thus activating the NIK/IKK cascade in the IL-1 signaling pathway (58). Hence, the signaling components NIK/IKKs are likely the key participants in *H. pylori*–mediated NF-κβ dependent MMP induction (48). This is consistent with the observations of *H. pylori's* role in modulating the expression of MMP 1, 7, 9, 10 (48, 59–61) by altering the NF-κβ binding activity in gastric cell lines (48) (Figure1).

Interestingly *cagA* dependent stimulation of MMP 10 is greatly complimented by EGFR activation (61). This might be accounted for, by the active participation of Src and ERK1/2 in *H.pylori*-induced MMP-10 expression, occurring downstream of EGFR activation (62, 63). The involvement of the JNK signal transduction pathway has been well documented (61).

3.3. MMP expression in NSAID induced gastropathy.

NSAID induced ulceration are observed in approximately 5% to 10% of the global population at least once in their lifetime (1). These are the second most common cause of gastric ulcers after *H.Pylori* infection (5, 64). NSAIDs restrict the synthesis of prostaglandin by inhibiting COX-1/2. This results in reduced bicarbonate production and gastric blood flow (65, 66). The inhibition of prostaglandin is also known to be associated with an intrinsic pathway which alters the level of MMP expression in gastric tissue (13, 50, 67). Interestingly, prostaglandin inhibition is just a part of the causative mechanism, responsible for NSAID induced ulcers in the gastric epithelial lining. The existence of a prostaglandin independent pathway which increases ROS production plays a crucial role in the modulation of MMP expression (68). This is usually associated with a number of consequential events like apoptosis and leukocyte infiltrations (69–71) which are generally observed upon exposure to NSAIDs.

3.3.1. Prostaglandin dependent pathway.

NSAIDs act through prostaglandin dependent pathway via COX inhibition (especially COX-2), to downregulate the expression of PGE2 and VEGF, both are vital in gastric protection and healing (50). PGE2 is known to be synthesized intramurally in the gastric mucosa during the churning of gastric contents. It protects the gastric mucosa from NSAID induced damage (72) and modulates the expression of MMP 2 through the pAKT pathway (73). Angiogenesis, a crucial phenomenon in gastric ulcer healing, is known to be promoted by VEGF (74), whose transcriptional activation is also maintained by PGE2 via Sp1 binding

sites on the VEGF promoter (75). Thus, downregulation of both PGE2 and VEGF is parallel to MMP2 suppression thereby leading to gastric lesions (50, 76).

3.3.2. Prostaglandin independent ROS mediated pathway.

NSAIDs promote the production of H_2O_2 which in turn acts as a mediator to inhibit the activities and gene expressions of MMP 2 and 14, respectively. However, H_2O_2 activates other MMPs by modulating the expression of cytokines and growth factors. The above-mentioned effect of NSAID on MMP expression occurs in a prostaglandin independent pathway which is mainly mediated by increased ROS (77). In this pathway, ROS activates NIK, an upstream kinase in the non-canonical pathway of NF-κB activation. Pro-MMP 1,3,7, 9 and 10 promoters are known to contain several NF-κB binding sites (78). Thus, activation of NF-κB triggers the overexpression of these pro-MMP genes which play an important role in the early stages of gastric ulceration (13, 77). Also, ROS is directly involved in altering the structure of MMPs which is also a major causative factor responsible for the onset of the gastric ulcers (77). Along with these, the NSAID administration also elevates TNF-α and IL-1 levels (79). TNF-α and IL-1, then, upregulate the expression of MMP-9 (11) and MMP-1 (80) in the ROS mediated pathway.

4. ACTIONS OF MELATONIN IN THE REDUCTION OF OXIDATIVE STRESS

4.1. Melatonin as a direct scavenger of free radicals.

Melatonin, like any other indoleamine, houses a certain type of thermodynamic and kinetic arrangement which facilitates it to be a very efficient and potent free radical scavenger. The antioxidant properties of melatonin greatly pertain to its way to react with the free radicals present in the cell of an organism. The kinetics of the reaction enables melatonin to work at very low concentrations (81). Melatonin is known to directly detoxify several ROS including hydroxyl radical ($^{\cdot}OH$), H_2O_2, superoxide anion radical (O_2^-), singlet oxygen ($^1O_2$) and hypochlorous acid (HOCl). While scavenging these ROS, melatonin converts them to potentially less harmful agents. At the same time, melatonin also has the capability of recycling itself thus, enabling it to continuously scavenge ROS (82–85). Thus melatonin becomes an indispensable member of the antioxidant family with a high propensity to detoxify ROS in a very effective manner (Table 2).

4.2. Influence of melatonin on antioxidant enzymes.

The antioxidant enzymes including glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) are known to maintain the redox balance of the cell by metabolizing ROS to relatively less harmful byproducts. Melatonin, on the other hand, is known to enhance the activity of these enzymes at relatively low doses. Melatonin's role in promoting glutathione homeostasis by stimulating the activities of GPx, glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PDH) is well documented (81). In addition, melatonin also stimulates the activity of γ-glutamylcysteine synthetase, the rate-limiting enzyme for glutathione biosynthesis (86). Administration of melatonin significantly upregulates the expression of both cytosolic and mitochondrial SODs. These are the most important members of the antioxidant family and they dismutate $O_2^{\cdot -}$ to H_2O_2 (87). This not only reduces the amount of O_2^- but also reduces the likelihood of a coupling reaction between O_2^- and $NO^{\bullet}$ to the highly reactive $ONOO^-$ (88). Although melatonin's influence on CAT the

peroxisomal enzyme to remove H_2O_2 has not been studied fully, although, Lopez *et al*. (89) have observed melatonin's protective role on CAT.

Table 2: A tabulation of some of the studies that have investigated the ROS scavenging activity of melatonin.

ROS	Research group	Source of radical	Method of measurement
$OH^{\cdot}$	Poeggeler *et al.* (90)	Fenton reagents	Spectrofluorometry
	Zang *et al.* (91)	Fenton reagents	EPR and spin trapping
	Marshall *et al.* (92)	$FeCl_3$-EDTA, Ascorbic acid and H_2O_2	Deoxyribose assay
H_2O_2	Tan *et al.* (85)	H_2O_2 solution	EI-MS, H-NMR, C-NMR Spectroscopy
	Pick *et al.* (93)	Phagocytic stimulation of macrophages	Phenol Red Assay
O_2^{-}	Zang *et al.* (91)	Hypoxanthine-xanthine oxidase system in presence of Cyt c or NBT	EPR Spin trapping measurements
$^1O_2$	Poeggeler *et al.* (90)	Photosensensitization of riboflavin	EPR Spin trapping measurements
HOCl	Dellegar *et al.* (94)	NaOCl solution	GC-MS, H-NMR Spectroscopy
	Chang *et al.* (95)	Quenching of β-carotene	Spectrophotometric Assay

4.3. Anti-inflammatory role of melatonin,

Oxidative stress and inflammation are closely related events. Melatonin, by influencing the activity of multiple antioxidant enzymes (20) are known to display anti-inflammatory activity in numerous tissues. Melatonin upregulates the gene expression of several anti-inflammatory enzymes while it downregulates the expression of the pro-inflammatory enzymes (96). Many studies have identified the inhibitory effect of melatonin on proinflammatory cytokines including IL-1 and TNF-α (97) and thus, protects against the inflammatory tissue damage during gastric ulceration (96). The anti-inflammatory function of melatonin is beneficial for chronic GI tract diseases (70).

5. GASTRIC ULCERS AND MELATONIN

Despite melatonin's discovery over 60 years ago, its potential role in preventing gastric ulcers was not unveiled until the last few decades (81). Certainly, its contribution in gastroprotection is well documented (96–98), which is further supported by the elevated expression of MT1 and MT2 receptors in the gastric mucosal tissue in an ulcerative condition (99). The exceptionally high levels of melatonin in certain segments of the gastrointestinal tract have been reported (100, 101). Melatonin's role in protecting the gastro-duodenal lining can also be attributed to its amphiphilic nature (18, 102, 103). This feature allows melatonin to freely access every compartment of the cell thus enabling it to scavenge the ROS induced by *H.pylori* infection or NSAID on site (104, 105). Melatonin preserves tissue prostaglandin

levels to reduce acid secretion, elevate mucous and bicarbonate secretion, enhance blood flow, thus, offers gastroprotection (70). It also stimulates post-ulcerative wound healing and imparts gastro-protection by different mechanisms (106-108).

Although PPIs are the most commonly prescribed drugs for gastric ulcers, these drugs come with a lot of shortcomings and can't be prescribed to some patients with certain underlying conditions like HIV and osteoporosis. As a result, several hospitals in the US have replaced PPIs with melatonin for treating certain gastric ulcers (109). Melatonin is effectively used with other drugs (omeprazole) and vitamins to possibly reduce the side effects of PPIs. Currently, several studies are being conducted in an attempt to completely replace PPIs with melatonin (109, 110).

5.1. Crosstalk between melatonin and MMP during ulcerative wound healing.

The role of MMP in the development of gastric ulceration is well-established and the mechanisms have been discussed above. Among the twenty-four isoforms of the enzymes, MMP 1, 2, 3, 7, 9, 10 and 14 have been extensively studied since these MMPs are closely related to the onset of gastric ulcers (11, 50, 60, 61, 89, 111). A sharp contrast can be observed in the expression pattern of these MMPs. For example, in a typical NSAID induced gastric ulcer, an approximately ten-fold rise was observed in the expression of pro-MMP 9 and similar patterns were also reported for MMP 3 and 10. However, the expression of MMP 2 and 14 are simultaneously downregulated. (50). The differential expression pattern of these MMPs are directly correlated with the remodeling of ECM and wound healing processes. Obviously, melatonin is capable of regulating the balance of MMPs primarily by targeting the expression of pro-MMPs and tissue inhibitor of metalloproteinases (TIMP) (112, 113). It downregulates the expression of pro-MMP 1, 3, 7, 9 and 10 by suppression of the IL-1β induced NF-κβ pathway (114). In addition, melatonin up-regulates SIRT-1. SIRT-1 can activate PGC-1α (115), in turn, PGC-1α strongly induces Nrf2 (116). Nrf2 is a key regulator that binds to ARE and regulates the gene expression of antioxidant enzymes (117,118). A recent study has also reported that Nrf2 induces the expression of Heme oxygenase 1 (HO-1) which is an important mediator of VEGF (119). The VEGF levels are parallel to the expressions of MMP-2 and also the antioxidant enzymes in an Nrf2 mediated pathway. Melatonin is a selective inhibitor for MMP 2 which has the opposite effect to MMP 1, 3, 7, 9 (105, 106) (Figure 2). Thus, melatonin will maintain the well-choreographed synchrony among MMPs and other intracellular components to reduce the gastric ulceration and promote its healing.

6. CONCLUDING REMARKS

This review summarizes the impact of MMPs on gastric ulcers induced by *H. pylori* and NSAID. Most importantly, we have discussed the potential mechanisms of how melatonin counteracts this disorder without altering the normal physiology. This is an important advantage of melatonin over other conventional medicines to treat gastric ulcers. In *H. pylori* and NSAID induced gastric ulcers, ROS formation is the culprit that triggers abnormal cell signaling, epigenetic changes, cellular injury and initiation of ulceration. Melatonin, on the other hand, scavenges ROS and balances the activities of different MMPs. Based on the results from *in vitro* and *in vivo* studies, we have concluded that melatonin is probably a promising therapeutic molecule in combating gastric ulcers and their subsequent manifestations. However, further studies are necessary to prove its utility in wound healing and other ECM related regenerative processes

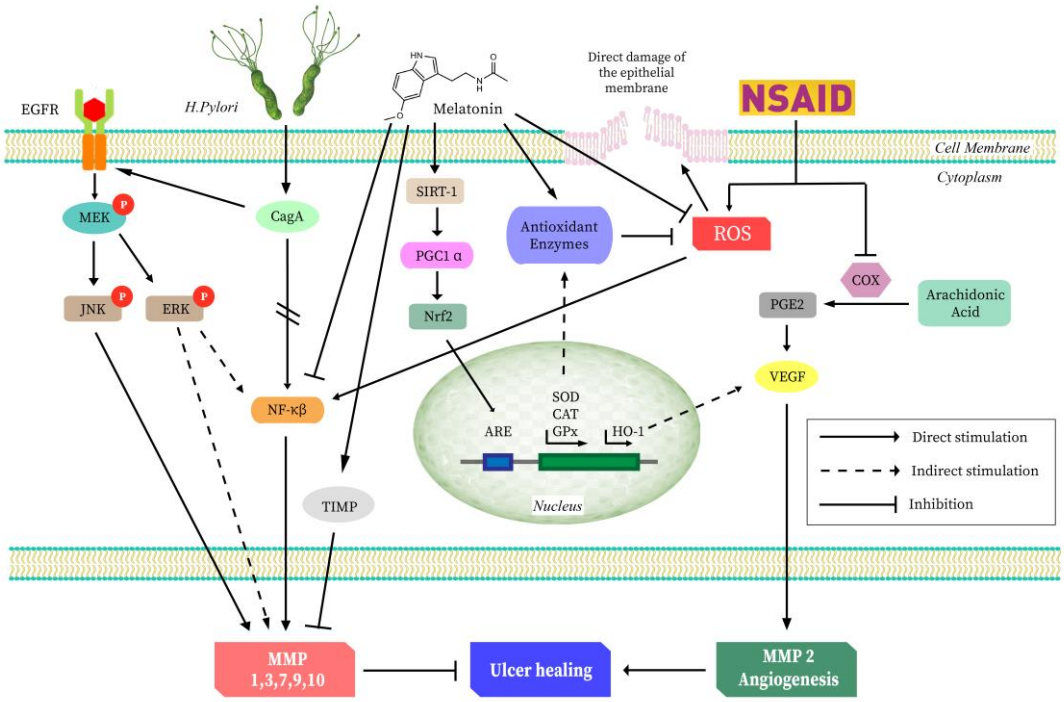

Fig 2. Potentially protective mechanisms of melatonin on NSAID and *H. pylori*-induced gastric ulcerations.

EGFR: Epidermal growth factor receptor, MEK: Mitogen-activated protein kinase kinase, JNK: c-Jun N-terminal kinase, ERK: Extracellular-signal-regulated kinase, CagA: Cytotoxin-associated gene A, NF-κβ: Nuclear factor-kappa B, SIRT-1: Sirtuin 1, PGC1α: Peroxisome proliferator-activated receptor-gamma coactivator 1α, TIMP: Tissue inhibitor of Metalloproteinase, ARE: Antioxidant response element, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase, HO-1: Heme oxygenase-1, COX: Cyclooxygenase, PGE2: Prostaglandin E2, VEGF: Vascular endothelial growth factor.

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AUTHORSHIP

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 in editing the manuscript.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

ABBREVIATIONS

$^1O_2$:	Singlet oxygen
ATP:	Adenosine triphosphate
ARE:	Antioxidant response element
Ca:	Calcium
CagA:	Cytotoxin-associated gene A
CAT:	Catalase
COX:	Cyclooxygenase
Cys:	Cysteine
ECM:	Extracellular matrix
EGFR:	Epidermal growth factor receptor
ERK:	Extracellular-signal-regulated kinase
G6PDH:	Glucose-6-phosphate dehydrogenase
GPx:	Glutathione peroxidase
GR:	Glutathione reductase
H. pylori:	Helicobacter pylori
HO-1:	Heme oxygenase-1
H_2O_2:	Hydrogen peroxide
H_2S:	Hydrogen sulphide
HOCl:	Hypochlorous acid
IKK:	IκB kinases
IL-1:	Interleukin 1
IL-1β:	Interleukin 1 beta
JNK:	c-Jun N-terminal kinase
MEK:	Mitogen-activated protein kinase kinase
MMP-	Matrix Metalloproteinase
NF-κβ:	Nuclear factor kappa B
NIK:	NF-κβ -inducing kinase
NO:	Nitric oxide
NSAID:	Non-steroidal anti-inflammatory drug
O_2^-**:**	Superoxide anion radical
OH:	Hydroxyl radical
PGC1α:	Peroxisome proliferator-activated receptor-gamma coactivator 1α
PGE2:	Prostaglandin E_2
PP1:	Proton pump inhibitor
ROS:	Reactive oxygen species
SIRT1:	Sirtuin 1
SOD:	Superoxide dismutase
Sp1:	Specificity protein 1
TAK1:	Transforming growth factor-β-activated kinase 1
TIMP:	Tissue inhibitor of Metalloproteinase
TNF-α:	Tumor necrosis factor alpha
VEGF:	Vascular endothelial growth factor
WHO:	World Health Organization
Zn:	Zinc

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