Review

Pleiotropic roles of melatonin against oxidative stress mediated tissue injury in the gastrointestinal tract: An overview

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ABSTRACT

The excessive production of free radicals and/or reactive oxygen species (ROS) in gastrointestinal (GI) tract leads to oxidative damages in GI tissues with development of varied pathological conditions and clinical symptoms. Many endogenous as well as exogenous factors are involved in such pathogenesis, herein, focus was given to the factors of metal toxicity, non-steroidal anti-inflammatory drugs (NSAIDs), ischemia-reperfusion, consumption of high fat diet and alcohol, and different pathological conditions and diseases. Since ROS is more or less involved in the GI damages caused by these factors, therefore attempts have been made to develop appropriate therapeutic agents that possess antioxidant properties. Being a potent antioxidant and free radical scavenger, melatonin was suggested as a potent therapeutic answer to these GI damages. The discovery of different binding sites and receptors of melatonin in the GI tissues further proves its local actions to protect these tissues from oxidative stress. In the review, we attempt to try our best to summarize the current developments regarding the GI injuries caused by oxidative stress and the potential beneficial effects of melatonin on these injuries. The important molecular mechanisms associated with these changes were also highlighted in the discussion. We hope that this review will provide valuable information to consider melatonin as a suitable molecule used for GI tract protection.

Keywords: gastrointestinal tract, oxidative stress, tissue damage, melatonin, antioxidant, protection

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1. INTRODUCTION

Oxidative stress plays a key role in the pathogenesis of varied clinical conditions caused by ROS (1-3). A growing body of animal studies clearly indicated the harmful effects of oxidative stress on pathogenesis in different organs including heart (4-5), liver (5), lung (6), muscle (7) and GI tract (2-3, 8-9). Among these, GI tract has drawn a great attention from researchers due to its

production of large amounts of ROS (1), particularly under ischemia/reperfusion event (10). In addition, harmful substances containing in the ingested food particles and pathogens would cause epithelium-associated intestinal inflammation to enhance the production of inflammatory cytokines and other mediators from the polymorphonuclear neutrophils and macrophages. These eventually further increase intracellular oxidative stress in GI tract (11). Other factors including heavy metal (12-16), non-steroidal anti-inflammatory drugs (NSAIDs) (3, 17), consumption of high fat diet (18) and alcohol (19), ischemia-reperfusion (20) and variety of diseases (11) also cause gastrointestinal injuries. Many more other harmful factors can be mentioned; however, the current review will focus on what we have mentioned above, which are more or less associated with GI tract oxidative stress.

Discovery of the free radical scavenging and antioxidant properties (21) of an essential amino acid tryptophan's derivative, melatonin, opens up a new avenue in the field of oxidative stress protection. Thereafter, identification of melatonin binding sites or its receptors in the GI tract has promoted the idea of melatonin's local actions in the GI tract (2, 22-25). Animal studies have provided further evidences to suggest that melatonin, by acting as a potent free radical scavenger (26) and/or by stimulation of different antioxidant enzymes (27), suppresses intra-cellular oxidative stress during inflammation (28-29). Inflammation *per se* also induces melatonin synthesis in GI tract and the synthetic activity of melatonin directly depends on the degree of inflammation in the GI tissues (24). Considering its location and functions, we hypothesize that melatonin may play a critical role in GI tract, particularly in protection of GI tract from the oxidative stress. These will be discussed below.

2. MODES OF OXIDATIVE STRESS INDUCED TISSUE DAMAGE IN THE GI TRACT

2.1. Endogenous stressors.

Despite of the fact that numerous endogenous stressors are involved in the excessive production of ROS (30), most studies are focused on the exogenously occurring oxidative stressors in the GI tract as illustrated in Fig. 1. Catecholamines, especially adrenaline, are endogenously occurring substances and they are released from sympathetic nervous system and adrenal medulla into the circulation to balance the normal physiological functions (31). However, due to their potent pro-oxidant and auto-oxidation properties, the uncontrolled and excessive release of adrenaline will generate enormous ROS which will cause harmful effects on the cell/tissue/organ (32-35). Adrenaline has been reported to cause mucosal erosion in mammalian GI tract (36). A recent *in vitro* study has confirmed the adverse effects of adrenaline in different GI tissues of rats (2). Briefly, adrenaline was found to decrease intracellular levels of necrosis factor-kappa beta (NF-kβ), but increased the levels of lipid peroxidation, protein carbonyl content, nitrate and inflammatory cytokines [tumour necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL6)]. Moreover, activities of different antioxidant enzymes were also enhanced following adrenaline treatment. The results demonstrated the capability of adrenaline in inducing oxidative stress by altering the antioxidative and inflammatory responses in GI tract (2).

2.2. Exogenous stressors.

2.2.1. Heavy metal toxicity.

To maintain a variety of biological functions, some heavy metals are essential at certain concentrations in organisms. However, they become toxic when their concentrations exceed threshold levels. Heavy metal toxicities were associated with various pathologies in animals (37). Not only heavy metals *per se* but their mixtures with other compounds possess toxicities in organisms (38). Earth crust enriches heavy metals but the pollution is mainly from industrial polluted ground water, mining, sewage sludge, commercial products, urban runoff, contaminated food chain and many others (39). One of the important mechanisms related to heavy metal toxicity is oxidative stress. In depth, these heavy metals, arsenic, lead, cadmium and mercury, hold the ability to generate a wide variety of ROS including superoxide anion ($O_2^{\bullet-}$), nitric oxide ($^{\bullet}NO$), hydroxyl radical ($^{\bullet}OH$). These ROS actively participate in metal toxicity and result in oxidative injury in lipids, proteins and DNA (40) which leads to gastrointestinal as well as neuro-, hepato-, nephro- and cardio-toxicities in humans and other vertebrates (5, 41-43). To better understand their toxicities, each of them will be discussed respectively.

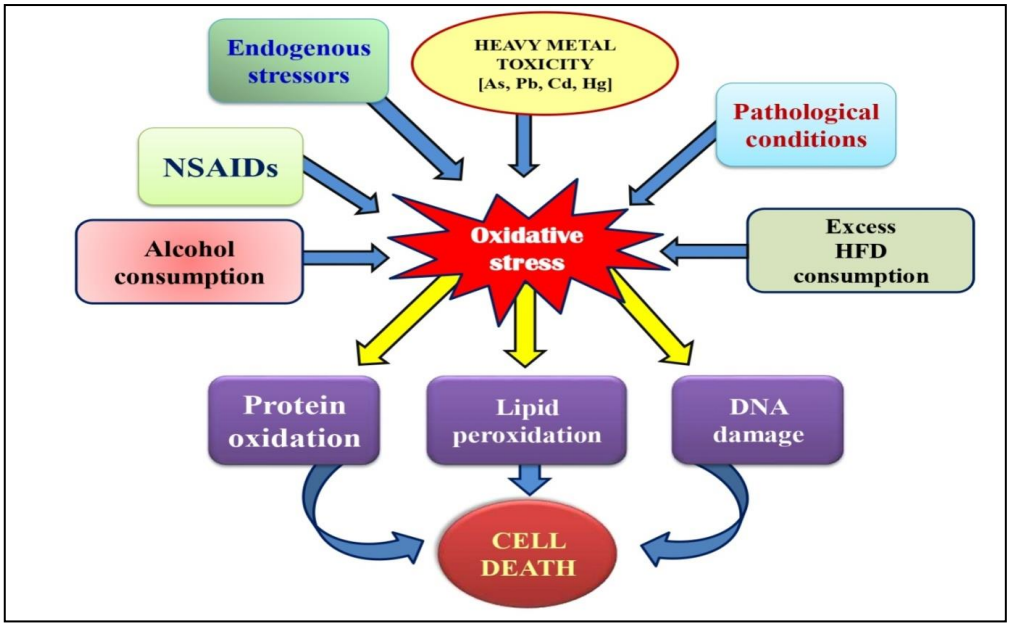

Figure 1: Schematic representation of the roles of different endogenous and exogenous stressors on gastrointestinal tissue injuries.

2.2.1.1. Arsenic (As).

As (also termed as protoplastic poison) is widely scattered in the environment that forms diverse chemical complexes in the body with its most common oxidation states of 5^+, 3^+ and 3^-. In nature, As exists as the organic, inorganic and arsine gas, of which inorganic and arsine gas are the most toxic chemical forms. Ingestion, inhalation and absorption through skin are the possible route of As exposure. The contaminated drinking water is the most common source. The estimated lethal dose of inorganic As is 0.6 mg/kg. In mammals, 80-90% absorption of As takes place in the GI tract and then, releases into the blood, where it binds with globin and thereafter is transported throughout the body (43-44). The fact that As causes excessive production of ROS and oxidative tissue injury has been well documented in humans and, its adverse effects on important organs of any individual exposed are devastating (45). As interacts with sulfhydryl group containing proteins and, therefore, jeopardizes functions of several enzymes which are

associated with cellular respiration, in some cases, it even disturbs mitosis (45). Arsenic increases $O2^{\bullet -}$, H_2O_2 and •OH to induce lipid peroxidation (LPO), and initiates apoptosis. The oxidative stress caused by As alters the activities of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and also non-enzymatic antioxidant i.e., reduced glutathione (GSH) possibly through the formation of monomethyl arsenous (MMA) compounds (45). Notably, covalent binding of As with the thiol group of nitric oxide synthases (NOS) produces monomethylarginine (MMA) compounds which promote the development of different gastrointestinal symptoms described as arsenicosis. Apart from serious GI irritation, As exposure also causes nausea, vomiting and diarrhoea (14). Clinical signs of acute As poisoning in GI tract include painful swallowing, nausea, thirst, burning lips, several abdominal colic, etc. Mechanism of As toxicity in GI tract is associated with epithelial oxidative damage (12). Flora *et al*. (41) have confirmed the association between the concentration of As and ROS, its interaction with NOS and modulation of signalling cascade pathway via mostly mitogen activated protein kinases (MAPKs). All these events collectively result in the induction of cellular toxicity and apoptosis.

2.2.1.2. Lead (Pb).

Pb is a ubiquitous toxic metal. The features of its ductility, malleability, dense, and corrosion resistance property have made this heavy metal be widely used. Pb is mostly used in the metallic product, battery production, X-ray device etc., leading to exposure of persons working in these industrial areas (46). According to the reference of World Health Organization (WHO), the tolerance of Pb intake should not exceed 25mg/kg/day, otherwise, it causes oxidative stress and organ dysfunctions in mammals (47). Pb has little physiological functions but causes oxidative stress in different vital organs including GI tract (13, 48). This is probably that Pb can mimic some trace elements such as calcium, iron and zinc as a cofactor of several antioxidant enzymes and various intracellularly enzymatic reactions (49). In addition, Pb inhibits glutathione reductase (GR), thereby disturbing the pathway for the conversion of oxidized glutathione (GSSG) to reduced glutathione (GSH), ultimately declines the level of GSH. It was reported that Pb promoted the production of delta-aminolevulinic acid dehydratase (delta-ALAD) which in turn increased the generation of ROS in organisms (50-51). When Pb was incubated with essential unsaturated fatty acid a significant augmentation of malondialdehyde (MDA) was reported (52). Similarly, Pb exposure has also been associated with a high risk of stomach cancer in humans (16). Collectively, Pb exhibits its ability to induce oxidative stress by generation of ROS and reactive nitrogen species (RNS) to damage structures and functions of cell membrane and DNA in different tissues and organs including GI tract in vertebrates (41, 49).

2.2.1.3. Cadmium (Cd).

Cd is a highly pollutant toxicant in the environment and is classified as type-1 human carcinogen by the International Agency for Research on Cancer of USA (53). Cd contamination is widely spread from nickel-Cd batteries, stabilizers, alloys, metal coating and also pigments. Ingestion and inhalation are the main routes of Cd exposure for either occupational or non-occupational persons. The biological life of Cd is around 17-30 years, therefore, it can be accumulated in its primary target organs (liver and kidney) and to some extent in the GI tract (43, 54). Although Cd is a non- Fenton reaction metal, but it generates $O_2^{\bullet -}$, H_2O_2 and ·OH indirectly by the replacement of some metals such as copper (Cu), zinc (Zn) and iron (Fe) which are required for catalytic function of several enzymatic reaction (5). In addition, Cd is reported to

induce oxidative stress through other mechanisms including depletion of GSH, binding with thiol-group containing proteins, altering activities of different antioxidant enzymes (SOD, CAT and GPx). It inhibits complex III of the mitochondrial electronic transport chain (ECT), thereby, disrupting mitochondrial membrane structure and triggering the onset of apoptosis (55). Such facts were confirmed by the observation that Cd contamination was found to increase the level of lipid peroxidation resulting in the disruption of proteins, lipids and DNA (56). Although both *in vitro* and *in vivo* studies indicated Cd participated in the induction of apoptotic pathways, but the exact mechanisms remain unclear (57).

2.2.1.4. Mercury (Hg).

Hg, a reactive transition metal, exists in a liquid form at room temperature. It however, also can form mercury vapour in the environment to make it be extremely toxic. Intoxication of Hg leads to the development of several disorders including Minamata, Hunter-Russell syndrome and acrodynia (pink disease) (15). Approximately 80% of mercury vapour is absorbed through inhalation and enters into the circulatory system to further distribute to whole body. Since the biological half-life of Hg is 7-10 days, it is cleaned up and metabolized more quickly than other heavy metal from the body (58). The chronic exposure of Hg even at very low concentrations (in the range 0.7–42 $\mu g/m^3$) will lead to toxicity in a variety of organs, especially GI tract with ulceration and hemorrhage (59). Hg has the great affinity binding to thiol group containing protein like GSH, cysteine and metallothionein (MT) and hence, increases cellular oxidative injury (60). Acute Hg exposure in the form of chloride generally targets GI tract resulting in necrosis of intestinal mucosa, vomiting, bloody diarrhea and abdominal pain possibly due to extensive precipitation of different enterocyte proteins (61).

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

Use of NSAIDs has been popular for several decades to treat excessive pain, fever and inflammation because of their anti-inflammatory, antipyretic, and analgesia features (3, 17, 62-63). Despite of the fact that NSAIDs such as sulindac, sulindac sulfide, sulindac sulfone, aspirin, indomethacin, acemetacin, tolmetin, etodolac, ketorolac, and oxaprozin exhibit diverse beneficial effects on inflammatory symptoms (64-66), but their uncontrolled use also cause serious complications in different organs, of which, GI tract (17) is the main target. The NSAIDs have varied half-life, high water solubility, detergent (67) and quick absorption properties that eventually increase their bioavailability in the GI tract (68). The high levels of NSAIDs initiate gastric tissue damages and bleeding which further promotes development and progression of inflammation and ulcerative symptoms (11, 69). Several NSAIDs also decrease mucosal microvascular blood flow that is critical in developing gastric ulcers. However, overproduction ROS plays a pivotal role in the development of NSAID associated gastric ulcerations (70-71). NSAIDs, such as aspirin, indomethacin and ibuprofen, inhibit the synthesis of prostaglandins and proliferation of cells, possibly by depleting cellular energy supply that eventually elevates the tissue levels of H_2O_2 and ·OH in the gastric mucosa leading to oxidative damage (70, 72-74). Indomethacin and piroxicam irreversibly inactivate gastric peroxidise and increase lipid peroxidation rate with concomitant decrease in the levels of antioxidant enzymes, finally leading to excessive production of ROS and gastric ulceration (1, 75). NSAIDs also causes mitochondrial injury by disrupting their transmembrane potential and increasing permeability of transition pore that results in cytochrome c leakage and ROS generation. Consequently, caspase cascade is active to enhance peroxidation of membrane lipids. All these lead to the naive cell

towards apoptosis (76). Such sequential responses of varied intracellular components enhance permeability of intestinal mucosa, development of mucosal erosion and the risk of gastric injuries (76).

2.2.3. Ischemia-reperfusion injuries.

Temporary interruption of intestinal blood flow by surgical procedures or, any other patho-physiological processes activate Toll-like receptors (TLRs) that eventually cause serious GI inflammation and tissue injury, a condition termed as ischemia reperfusion (I/R) (20). Actually, re-entry of oxygen to ischemic intestinal tissue results in reperfusion injuries which causes more damage than that of ischemia alone (77) due to massive accumulation of activated neutrophils and ROS (78). High level of oxidized glutathione (79) and the protective role SOD in the I/R tissues suggest a critical role of ROS during I/R induced pathogenesis in the GI tract (10, 80). Similarly, ischemic colitis occurs either due to blood clot induced reduction of blood flow (occlusive), constriction of blood vessels or low systemic blood pressure (non-occlusive) (81). The ischemic colitis also causes lipid peroxidation followed by sepsis and ulceration (82). Results from electron spin resonance spectrometry and low level chemiluminescence identified the occurrence of a sudden burst of oxidation immediately after 2–5 min of reperfusion in ischemic GI tissue (83). The burst of oxidation possibly is derived from multiple sites of mitochondrial ETC (84-85), metabolism of xanthine oxidase (86), endothelial NADPH oxidase (87), prostaglandins (88) and activated neutrophils (89).

2.2.4. High-fat diet.

Regular consumption of high-fat diet (HFD) leads to obesity, cardiovascular disease, dyslipidemia, non-alcoholic steatohepatitis, non-alcoholic fatty liver and insulin resistance along with inflammation and cancer (90-92). It is well documented that innate immune cells stimulated by HFD leads to a transient postprandial inflammation which modulates the intracellular status of inflammation (91-92). Since GI tract is a prime site for HFD induced inflammation, the importance of GI tract on human health has gained a great attention (18). Several studies have pointed out that obesity with HFD may associate with inflammatory changes in GI tract (18). HFD increases the amounts of chylomicrons in the intestine and also changing the composition of gut microbiota which have the direct association with obesity (93). Myeloperoxidase (MPO) is a crucial enzyme responsible for O_2 dependent microbial phagocytic activity in the intestine. Intestinal inflammation is associated with elevated level of MPO in the ileum which ultimately induces infiltration of polymorphonuclear neutrophil and macrophage and the overproduction of pro-inflammatory cytokines (TNF-α) (93). de La Serre *et al.* (93) also demonstrated that increased level of MPO enzyme activity, indirectly increases the activation of TLR4, which further suggests the activation of inflammatory response due to enhancement of enterobacteria. The imbalance between the intracellular levels of antioxidants and oxidants is also potent factor for intestinal inflammation induced by HFD. This imbalance is due to overproduction of inducible nitric oxide synthase (iNOS) which in turn alters permeability of the intestinal membrane (94). Moreover, mitochondria are the primary source of ROS (95), which increases the lipid peroxidation to initiate an intermediate chain reaction to form more O_2•- and other ROS (96-97). HFD elevates circulatory free fatty acid (FFA) which then either enters in the mitochondria for oxidation or, is esterified to form triglycerides (TG), thus, increasing the mitochondrial β-oxidation and production of ROS (98). However, the exact pathway responsible

for these changes is unclear, and further studies are required to address HFD induced oxidative stress in the GI tract.

2.2.5. Alcohol consumption.

Alcohol can be generated *in vivo* from the pyruvate to acetaldehyde by alcohol dehydrogenase (98). In GI tract, a significant amount of ethanol is from diet and mainly metabolized in the liver. On other hand, ethanol can also be oxidized into carbon dioxide (CO_2) and water (H_2O) in the GI tract (99). Consumption of alcohol reduces the metabolism of certain bile-acids and may affect the intestinal microbiota (100). Acute and chronic consumption of alcohol induces oxidative stress by the generation of ROS and disturbs cellular antioxidant levels. Ethanol intoxication increases the production of carbon-centred radicals and H_2O_2, leading to the dysfunction of endothelium, ischemia of gastric mucosa and microcirculatory disorders (19). Consequently, ROS generated by alcohol modulates or damages the structural proteins, lipid molecules and DNA that in turn inactivates numerous enzyme transporters, transcriptional machinery, etc. Excessive production of ROS ultimately increased the level of lipid peroxidation, an indication of tissue damage, possibly by activation of different enzymes, viz., alcohol dehydrogenase, cytochrome P4502E1 (CYP2E1), aldehyde dehydrogenase and catalase (101). Additionally, oxidative stress induced by alcohol suppresses the activity of first line defense antioxidant enzymes, such as Cu-Zn SOD and Mn-SOD in cytosol and mitochondrial matrix, respectively (102).

2.3. Pathological conditions and diseases.

GI tract serves as one of the major sites for ROS generation to possess epithelial lining as a protective barrier for pathogens. GI tract directly contacts with the ingested food and pathogens which are causative factors of inflammation by activation of epithelium, polymorphonuclear neutrophils and macrophages. These immune cells generate inflammatory cytokines and other cellular mediators causing overproduction of intracellular ROS. The oxidative stress leads to development of numerous pathophysiological conditions including gastric ulcers, diverse malignancies and diseases (11). Some disorders which amplify the level of ROS in the GI tract promoted the vicious cycle to increase the severity of these diseases (11).

Gastroesophageal reflux disease (GERD) associated factors (acid, bile and inflammation) are found to increase the level of ROS either by decreasing endogenous antioxidants or, enhancing the expression of ROS-inducible genes or, both (103). In case of Barrett's esophagus and esophageal adenocarcinoma, unconjugated bile acids are known to act as potent cyclooxygenase-2 (COX-2) inducer which in turn induces ROS generation and activates the PA3K/AKT and ERK1/2 pathways (104). Similarly, levels of lipid peroxidation and 8-hydroxy-deoxyguanosine (as oxidative stress markers) are reported to be elevated in tissues of esophageal squamous cell cancer (105). Moreover, the reduced levels of SOD are evidenced to increase ROS accumulation in most of the gastroduodenal inflammatory diseases (106-107). On the other hand, phagocytic leukocytes seem to be the prime source of ROS generations in chronic inflammatory diseases, such as *Helicobacter pylori* induced gastritis and Irritable Bowel disease (IBD). Inflammation induced infiltration of neutrophils and macrophages in the gastric mucosa leads to overproduction of ROS, thus worsening the symptoms in the GI tract (11).

In majority of the peptic ulcer disease and gastritis, *H. pylori* is known to play key role by inducing non-phagocytic NADPH oxidase and altering proinflammatory cytokine production, thus enhancing the production of ROS in the gastric epithelial pit cells (108-111). The elevated

mucosal level of ROS was observed in patients with duodenal ulcer and severe duodenitis (112). On the other hand, enhanced lipid peroxidation along with decreased GSH levels clearly suggested that depletion of endogenous antioxidants may also lead to gastric ulcers (113-114). Prolonged exposure to ROS triggers genome damage and leads to uncontrolled activation of proto-oncogenes, mutations in oncogene/tumor suppressor gene and chromosomal aberrations (11). In case of IBD, inflammation induced phagocyte accumulation results in generation of $O2^{\cdot -}$, H_2O_2, and HO·, thus increases the risk of further tissue damage by enhancing membrane lipid peroxidation (115-116). Noteworthy, enteric commensal bacteria associated with the epithelia produce massive ROS that eventually alters/disrupts different intracellular proteins responsible for regulating diverse signalling pathways and affects various physiological functions of the host cell (117). Thus, involvement of ROS in the diverse gastrointestinal diseases is well documented; however, the exact underlying mechanisms are not clearly understood yet and require further investigations.

3. PREVENTIVE STRATEGIES

In order to minimize or, protect the tissue damage of GI tract from varied stressors, numerous approaches have been adopted so far, but all of these attempts remain to be improved for their efficacy. Some of the approaches are discussed herein.

3.1. Chelation therapy against heavy metal toxicity.

The principle of chelation therapy is to remove heavy metals from the body by different chelating agents. Some of them are discussed herein. The 2,3-dimercaptopropanol (BAL; also known as British Anti-Lewisite) is clinically used to treat patients with diverse metal toxicities (118). BAL chelates various toxic metals including inorganic mercury, antimony, bismuth, cadmium, chromium, cobalt, gold, and nickel, to form the stable products *in vivo* (118). However, profound side effects of BAL have restricted its use in mammals (119-120). 2,3-Dimercapto-1-propanesulfonic acid (DMPS) and its sodium salt (unithiol) are reported to be potentially chelating agents of different heavy metals. In children, DSMPS was found to effectively reduce the circulating level of lead (121) possibly through the organic anion transport system (122). The similar chelating properties were also reported for meso-2,3-dimercaptosuccinic acid (DMSA), calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) (123). In addition, *α*-lipoic acid quenches ROS under both *in vitro* and *in vivo* systems (124-125); it also chelates a variety of heavy metals (such as iron, copper, mercury, and cadmium), thus protecting different cells/tissues damage from oxidative stress (124, 126). However, none of these approaches has been tested in the gastrointestinal tissues under heavy metal toxicity.

3.2. Use of antioxidants against heavy metal toxicity.

The popular antioxidant vitamin E was used for this purpose (128). It reduces several transition metals, for example cupric ions (Cu^{2+}) to cuprous (Cu^{1+}) and ferric ions (Fe^{3+}) to ferrous (Fe^{2+}) and vitamin E was found to be effective against silver (118) and lead (128) induced cell/tissue damage. In Cd intoxicated tissues, vitamin E not only reduced the accumulation of Cd and rate of lipid peroxidation but also restored the levels of different endogenous antioxidants, clearly indicating its antioxidant properties against Cd toxicity (129). N-acetylcysteine or, N-acetyl-L-cysteine (NAC), another antioxidant, protected against toxicities from different heavy metals in organs of mammals (130-132). Interestingly, several plant

extracts were also found to be effective in protecting tissues from oxidative stress induced by heavy metals. For example, aqueous extracts of bark of *Terminalia arjuna* (5), curry leaf (*Murraya koenigii*) (133) and tulsi leaf (*Ocimum sanctum*) (134) were reported to act as potent antioxidants in protecting diverse mammalian tissues from Cd toxicity. Their effects in GI tract remain to be tested.

3.3. Development of alternatives for NSAIDs.

As to NSAIDs, several novel alternatives have been developed with expected no or least side effects, but ultimately these new products have still failed for the expectation to reduce their gastric ulcerogenesis (135). For example, nitric oxide (NO) is a potent vasodialator and inhibitor of neutrophil activation, thus, the NO moiety was incorporated into the classic NSAIDs to form NO containing NSAID (NO-NSAIDs) which is supposed to overcome the mucosal injuries (136). The NO-NSAID and its derivatives were unable to reduce the suppression of gastric prostaglandin synthesis and thus, it had limited effect on GI mucosal injuries (137-139). Similarly, the combination of a prostaglandin analogue and NSAID was used, but such attempt was finally neglected due to the severe side effects (140). Numerous other attempts have been made. These include enteric coating technology, parenteral administration, development of pro-drugs, synthesis of basic molecules and co-administration with prostaglandins or, acid secretion inhibitors or, cyclooxygenase-2 (COX-2) inhibitors (141-142), but none of them was recommended due to their unwanted reactions and gastric bleeding properties. Although synthesis and application of any potent antioxidant (such as cysteamine) tagged amide derivatives of different NSAIDs (for example diclofenac acid, tolfenamic acid, ibuprofen and indomethacin) were reported to reduce or, overcome the gastric ulcerogenesis in different mammalian models, further study for human application is required (3).

4. MELATONIN: AS A POSSIBLE THERAPEUTIC ANSWER TO OXIDATIVE STRESS

Melatonin passes through any biological membrane into cell/tissue/organ with ease due to its lipophilic nature and its specific transporters (2, 3, 26-27, 143). This advantage blesses this potent antioxidant to protect diverse cell/tissue from oxidative damage (144-145). Melatonin is highly effective to scavenge the most reactive and harmful •OH (21). Notably, uniqueness of melatonin lies in its pleiotropic actions on cells/tissues that marks its difference from other classic antioxidants. Apart from serving as a direct broad-spectrum antioxidant (21) melatonin also upregulates antioxidant enzymes and downregulates pro-oxidative enzymes to function as an indirect antioxidant (27). Therefore, it is necessary to evaluate the functional potentiality of melatonin in regulation of intra-cellular oxidative status in diverse cell/tissues/organ. Among them, GI tract (1-2, 8-9, 71, 146) has become the favorite site of research (144). This is also the focus of this review.

Antioxidant actions of melatonin on its target cell/organ under oxidative stress environment are conferred through two principle pathways, the receptor-independent and receptor-dependent ones (1, 27, 147). Such conclusion was derived from the observations that melatonin directly interacts with ROS and also upregulates the levels of mRNA and activities of different antioxidant enzymes including SOD, CAT, GPx, GSH, GR, glucose-6-phosphate dehydrogenase (G6PD) and gamma-glutamylcycteine synthase under oxidative stress (27, 144, 147). The details are described following.

4.1. Receptor dependent actions of melatonin.

Confirmation of the paracrine actions of melatonin in the GI tract came from the identification of melatonin specific receptors and/or its binding sites in the intestines of vertebrates (24-25) and the participation of GI derived melatonin in regulation of peripheral circulation of GI tract (24, 71, 148). Furthermore, melatonin was found to interact and activate its membrane receptors in GI tissues. Melatonin acts primarily through the two G-protein coupled membrane receptors- MT1 and MT2; however, another receptor MT3 (human quinone reductase 2) is also known to involve in melatonin signalling (149). Apart from its membrane receptors, melatonin also binds to its nuclear receptors which belong to the RZR/ROR orphan receptor family. Melatonin nuclear receptors have three subtypes- α, β and γ, of which α subtype possesses another four splicing variants (150). Activation of these receptors conveys the signal of melatonin to its target cell, thus exerting its physiological as well as pharmacological effects as a pleiotropic molecule (151). MT1 receptor activation stimulates G proteins; however, the same signal inhibits cAMP signalling pathways (152). In contrary, activation of MT2 receptor regulates phosphoinositide signal transduction pathways with the inhibition of the pathways associated with adenylyl cyclase and guanylyl cyclase (152). Under oxidative stress, melatonin acts on these receptors to activate/inhibit these receptors, respectively to precisely regulate the activities as well as expressions of a variety of antioxidant and prooxidant enzymes. The outcomes are to enhance the synthesis of other endogenous antioxidants and to reduce ROS formation. All these render its indirect antioxidant activity (27). For example, melatonin upregulates the activities of SOD, CAT, GPX, glutathione reductase (GR), glucose-6-phosphate dehydrogenase (G-6-PD) and gamma-glutamylcycteine synthase during stressful conditions (27).

4.2. Receptor independent actions of melatonin.

Melatonin can directly scavenge the highly toxic peroxynitrite anion, hydroxyl-, peroxynitrite-, and peroxyyl radicals (95, 143-144, 153). It can also quench singlet oxygen (95, 153) to protect membrane lipid peroxidation (154) under both acute and chronic inflammation (155-156). Such free-radical scavenging activity of melatonin does not require any receptor at the target cells. The results from numerous *in vitro* and *in vivo* studies have unequivocally proven the potent direct antioxidant properties of melatonin (155, 157-158). Interestingly, metabolites of melatonin generated from interaction with ROS also possess strong antioxidant properties. These metabolites are not only capable of scavenging highly toxic hydroxyl radical, peroxynitrite anion and peroxy radical, but also quenches singlet oxygen (153, 156, 159). Notably, these melatonin metabolites can cooperate with other antioxidants to maximum their protective effects on integrity of cellular membranes under oxidative stress (154, 160).

4.3. Abundance of melatonin in the gastrointestinal tract.

Melatonin was first reported to be present in the GI tract of rat (161) and mainly localized in the enterochromaffin cells (EC) of the digestive mucosa. These was identified by immunohistological techniques (24, 161) and quantified by radioimmunoassay (RIA) and high performance liquid chromatography (162-164). The auto-radiographic studies depicted its maximum binding in the mucosa and intestinal villi (165). At the sub-cellular level, strongest melatonin binding was found in the nuclear, followed by the microsomal, mitochondrial, and cytosolic fractions (166-167). The arylalkylamine-*N*-acetyl transferase (AANAT), the rate limiting enzyme in melatonin biosynthesis, was confirmed in the GI tract of numerous vertebrates (2, 8, 168-171). Interestingly, hydroxyindole-O-methyltransferase (HIOMT), the last

enzyme in melatonin biosynthesis pathway, was also detected in the digestive mucosa (172). Collectively, all these observations confirmed the presence of endogenous melatonin biosynthesis in the cells of the GI tract.

The biosynthetic process of melatonin in the GI tract is the same as in the pinealocyte with four-steps. First, GI tract cells take up L-tryptophan (Trp) from the circulation and convert it to 5-hydroxy-Trp (5-HTP) by the enzyme Trp-5-monooxygenase or, hydroxylase (173). Thereafter, 5-HTP is decarboxylated to form serotonin (5-hydroxytryptamine, 5-HT) by L-aromatic amino acid decarboxylase (174). Then, AANAT acetylates 5-HT to form N-acetyl serotonin (NAS) (175). Finally, NAS is O-methylated by the enzyme- HIOMT to form melatonin (176).

4.4. Melatonin protects gastrointestinal tissue from oxidative damage.

Melatonin is found to protect individuals from Cd-induced neurotoxicity either by inhibiting the imbalance in mitochondrial fusion and fission (177-178), or by inducing transcription factor EB- mediated autophagy (179). Melatonin also prevents toxicities of Hg (180) and As (181) in different tissues and organs. However, information regarding the protective effects of melatonin on heavy metal toxicities in gastrointestinal tissues is scarce. A study has reported the ameliorative effects of melatonin on Pb-induced oxidative damage in the stomach and duodenal tissues (182) and it showed that exogenous administration of melatonin decreased the levels of lipid peroxidation and protein carbonyl content, restored the activities of different endogenous antioxidants and preserved their histological structures in rats treated with Pb (182).

The protective effects of melatonin in the GI tissue against diverse oxidative stressors promoted the idea that melatonin may also have protective effects on NSAID associated gastric injuries (Fig. 2). The data of melatonin on injuries caused by a variety of stressors in the GI tract (71, 146, 183-184) suggested the potentially beneficial effects of melatonin against NSAID-induced gastric tissue injury. Actually, melatonin exhibited preventive effects on gastric damages caused by indomethacin, aspirin as well as piroxicam (185-186). A concomitant increase in circulating melatonin with aspirin induced acute gastritis indicated an inducible feature of melatonin synthesis in GI tract under oxidative stress, which is supposed to accelerate the ulcer healing process (185). In the case of diclofenac induced intestinal damage, application of melatonin improved the intestinal permeability status and restored mucosal integrity (187-188), possibly through the restoration of membrane potential and energy metabolism in the mitochondria, thus, reducing apoptosis (189).This is supported by melatonin to reduce electron leakage from the ETC and to elevate mitochondrial respiration and synthesis of ATP by promotion of the activities of complex I and IV (95, 147, 190). On other hand, melatonin prevents proteins, lipids and DNA from oxidative damage (144, 191-192). Moreover, melatonin enhanced the activities of gastric peroxidise, SOD and catalase to decrease of •OH (193) and reduces the NSAID induced oxidative damage in GI tract (194).

Among the diverse actions of melatonin in the GI tract, its protective roles against ischemia-reperfusion induced intestinal injuries were also documented. Administration of melatonin prior to ischemia or in the initiation of reperfusion in the intestinal tissues reduced the deleterious effects by over-production of ROS and/or RNS (71, 146, 183, 195-199). In different pathophysiological conditions, administration of melatonin not only suppressed gastric injuries, but also promoted its healing process through MT2 mediated pathway. In brief, MT2 activation enhances the expression of matrix metalloproteinase-2 (MMP-2), while it decreases the levels of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinases-2 (TIMP-2), thus reducing the endogenous level of ROS in the GI tissue (200-201). Several other mechanisms also

contribute to the protective effects of melatonin on GI tract. For example, melatonin inhibits secretion of gastric acid and infiltration of neutrophils, promotes mucosal blood flow into ulcer bed, bicarbonate secretion in the duodenum, and prostaglandin synthesis (186, 202-203). These are illustrated in Figure 2.

4.5. Melatonin as a potent anti-inflammatory agent in the GI tract.

Apart from being a potent antioxidant, melatonin is also an important anti-inflammatory agent in different organs including the GI tract (204-211). NF-kβ, a crucial transcription factor highly sensitive to oxidative stress, upregulates expression of several pro-inflammatory genes to induce a variety of cellular responses associated with inflammation (205, 209, 212). Melatonin can modulate NF-kβ signalling pathways to exert its anti-inflammatory role (206, 209, 213-214). Under diverse pathophysiological conditions, melatonin suppresses the intracellular levels of different pro-inflammatory cytokines including IL-1β, IL-2, IL-6, interferon-gamma (IF-γ) and tumor necrosis factor (TNF)-alpha, while it enhances the expression of anti-inflammatory cytokines IL-10 and tumor growth factor-β (207, 209, 215). Thus, melatonin counteracts inflammation associated intrinsic apoptotic pathway (216) in the GI tract. In addition, melatonin protects the endothelial cells from LPO-induced overproduction of NO by inhibiting the expressions of iNOS and cyclooxygenase-2 (COX-2) (217, 219). However, further studies are essential to elucidate the anti-inflammatory role of melatonin against diverse modes of inflammation.

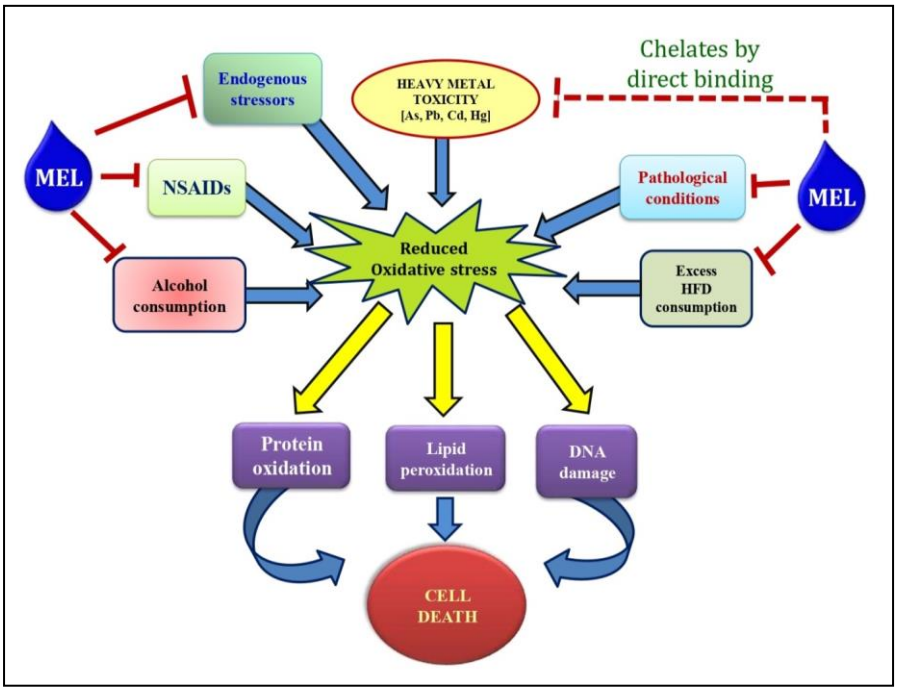

Figure 2: Schematic representation of the protective roles of melatonin on gastrointestinal tissue injuries caused by different endogenous and exogenous stressors.

5. FUTURE PERSPECTIVES

Collectively, these factors discussed above cause GI damage by a common feature that they enhance the production of intracellular ROS. Many attempts have been made to overcome the oxidative stress and GI injuries caused these factors, however, none of these attempts have

matched the expectation. It seems that if an antioxidant also exhibited anti-inflammatory activity it would be the suitable candidate for this purpose. Melatonin in this regard is an ideal molecule. It is a potent free radical scavenger with anti-inflammatory property; in addition, it has no, or low cytotoxicity. From this point of view, melatonin would be one of the best molecules to fight the gastrointestinal tissue injury associated with oxidative stress. To understand the protective mechanisms of melatonin in the molecular level requires further well-designed investigations.

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AUTHORSHIP

Dr. DB and Dr. AC revised the manuscript critically and approved it. Dr. PKP contributed to conception, prepared figures, drafted the manuscript and edited it. BB contributed in drafting of manuscript.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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