Review

Melatonin as a potential therapeutic molecule against COVID-19 associated gastrointestinal complications: An unrevealed link

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ABSTRACT

Outbreak of the novel coronavirus disease (COVID-19) was first reported in Wuhan, Hubei province of China, in early December 2019 which was later declared as a pandemic by World Health Organization (WHO) in March 2020. The International Committee on Taxonomy of Viruses has termed this novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the report of WHO on 29th April, 2020, 3018681 confirmed cases along with 207973 deaths have been documented globally. COVID-19 was originally reported as a lethal lung disease with fever and cough as the most common symptoms; however, the increasing number of gastrointestinal symptoms, such as diarrhoea, vomiting and abdominal pain in patients have clearly suggested that gastrointestinal tract (GIT) may also serve as a potential route for SARS-CoV-2 infection. To identify the effective therapies on this pandemic is urgent. Keeping this in mind, we realize that melatonin is a potent antioxidant, anti-inflammatory and immunomodulatory molecule and it has been used in diverse diseases and pathophysiological conditions, including respiratory disease and viral infections. Importantly, melatonin specific receptors and its endogenously synthetic machinery are distributed throughout the mammalian gastrointestinal system. Therefore, the therapeutic potentiality of melatonin in SARS-CoV-2 associated digestive symptoms cannot be ignored. In this review, we focus on the clinical implications of melatonin on the digestive complications associated with SARS-CoV-2 infection.

Key words: COVID-19, SARS-CoV-2, digestive complications, melatonin, gastrointestinal tract, inflammation, antioxidant, immunoregulator.

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1. INTRODUCTION

Emergence of a novel coronavirus, belonging to the family coronaviride, pneumonia was first reported in Wuhan, Hubei province of China, in early December 2019 (1-3). Following virus isolation and identification from human airway epithelial cells, International Committee on Taxonomy of Viruses (ICTV) has designated this novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 7th January, 2020 (1, 4, 5). World Health Organization (WHO) named this pneumonia as coronavirus disease 2019 (COVID-19) on 11th February, 2020 (2) and declared it as a pandemic on 11th March, 2020. Although most

of the coronavirus are harmless to human but beta coronaviruses, SARS-CoV (6) and Middle East respiratory syndrome coronavirus (MERS-CoV) (7) repeatedly cause lethal respiratory diseases in humans and their non-segmented positive sense RNA are mostly distributed in diverse mammals, including human (1, 8, 9). Till to 29th April, 2020, globally 3018681 confirmed cases along with 207973 deaths have been documented by WHO. Despite of the fact that COVID-19 was reported as a lethal lung disease with fever and cough as the most common symptoms (9, 10), the increasing number of gastrointestinal symptoms, such as diarrhoea, vomiting and abdominal pain in patients (2-10%) have implicated that SARS-CoV-2 might also utilize the digestive systems as a route of infection (9-12). This potential GI route infection has been masked by the profound respiratory symptoms occurred in the COVID-19 patients until to a single-cell transcriptomic study which has demonstrated this route of SARS-CoV-2 infection (13-14).

Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan derivative, is well known for its multiple physiological activities and it has been used to treat diseases and pathophysiological conditions related to virus infections, particularly to virus associated respiratory diseases (15-18). Therefore, under the current pandemic situation, testing of the potential effects of melatonin on respiratory and other symptoms associated to SARS-CoV-2 is encouraged. Interestingly, melatonin binding sites or its receptors and its endogenously synthetic machinery are distributed throughout the entire mammalian GIT (19-20). This suggests the local actions of melatonin as a potent anti-oxidant, anti-inflammatory and immuno-modulatory molecule (18, 21-22). Herein, based on the available information we hypothesize that melatonin, especially the gastrointestinal original one, may play a critical role in the prevention and treatment of SARS-CoV-2 associated gastrointestinal symptoms. Under current situation, this hypothesis warrants careful examination.

2. GASTROINTESTINAL TRACT: A POTENT TARGET OF SARS-CoV-2

Based on the clinical evidence gathered till date, it is clear that although SARS-CoV-2 primarily affects the respiratory system but its pathogenicity is not confined to the lungs only, rather it also damages other vital organs in critically illed patients leading to multiple organ dysfunction syndromes (23-25). Usually, coronavirus attacks the upper respiratory, gastrointestinal and central nervous systems in mammals (26). Specific to SARS-CoV-2, the gastrointestinal tract is also its common route for invasion. This has been confirmed in afflicted patients with digestive symptoms including, most commonly, anorexia and diarrhoea (3, 13, 27, 28).

Intestinal epithelial cells serve as a potent barrier in protecting against microbial infection by initiating immune responses (29). Viruses, such as coronavirus, rotavirus and noroviruses, prefer to attack the absorptive enterocytes and damage the normal absorption process that causes imbalance in intestinal secretion and activates enteric nervous system (30-32). This has been observed also in SARS-CoV-2 infection since this virus is detected in the oesophagus, stomach, duodenum and rectum, even in the faecal samples (52.4%) of COVID-19 patients (3). Moreover, detection of SARS-CoV-2 RNA in the stool of COVID-19 patients further confirms this contention (28, 33-35). The presence of viral replication in the susceptible intestinal cells, particularly in angiotensin converting enzyme-2 (ACE2)- and transmembrane protease serine 2 (TMPRSS2)-expressing oesophageal upper cells and absorptive enterocytes leads to GI symptoms (diarrhoea and nausea) 24-48 hrs prior to the appearance of fever and respiratory symptoms in some patients (14, 36, 37). In severe cases, SARS-CoV-2 even binds and manipulates the expression of ACE2 in hepatic tissue causing liver injuries (11). On the other hand, SARS-CoV-2 can modify the performance of microflora in GIT and such alterations can interfere respiratory system and vice versa (via

"gut-lung axis"), possibly through the mucosal immune system (38, 39). Collectively, the increasing GI symptoms in COVID-19 patients probably indicates profound elevation in viral load as well as their replication in the GI cells which eventually increases the disease severity (36).

3. TRANSMISSION OF SARS-CoV-2 IN THE GASTROINTESTINAL TRACT

In general, direct contact or air droplets are the principal route of SARS-CoV-2's human-to-human transmission (1, 2, 37) since person's contact within the distance of 1 meter from each other shows the maximum risk of SARS-CoV-2 infection (40). Although the exact pathway or route through which SARS-CoV-2 infects the GIT is still not clarified, some clues are present. The co-expression pattern analysis of single-cell RNA sequencing data indicates that the SARS-CoV-2 virus enters into the host intestinal cells by interacting with ACE2 and TMPRSS2 as the receptors which are located in the cell membrane. The cells that express both the receptors are the most vulnerable for SARS-CoV-2 infection, while cells which only express one of the receptors are more resistance to this virus attack (14, 41-43). For example, COVID-19 patients usually have elevated co-expression of ACE2 and TMPRSS2 in the oesophageal upper epithelial and gland cells, and absorptive enterocytes of the ileum and colon (14, 42). These observations addressed the importance of both ACE2 and TMPRSS2 receptors in the pathogenesis of COVID-19 (43). It reveals, for the first time, the possibility of extra-pulmonary spread of SARS-CoV-2 in the infected individuals (14, 42). In addition, the virulence of SARS is also associated with increased permeability to intestinal lipopolysaccharide and bacterial transmigration through the gastrointestinal wall (44).

Transmissibility and pathogenesis of coronavirus in human are primarily a resultant of an interaction cascade, i.e., - virus first attaches to the host cell followed by recognition of specific receptor, then cleavage by protease and fusion with membrane, finally its transmembrane spike glycoprotein (S-protein) binds to cell specific receptor (ACE2 and TMPRSS) -binding domain and enters into cells (12). ACE2 is a zinc metallopeptidase that converts angiotensin II to angiotensin I-VII (1, 12, 14, 43). The property of ACE2 to interact with a predetermined receptor-binding domain of CTD1 in SARS-CoV promotes its efficiency in spreading the infection among species, thus increasing person-to-person transmission (45, 46). Different configurations ('up' and 'down') of CTD1 facilitate binding to ACE2 by controlling the interaction between CTD1, CTD2, S1-ACE2 complex and the S2 subunit (47). Structural analysis of SARS-CoV-2 S protein revealed its higher binding affinity to ACE2 than that of SARS CoV S protein (37, 48, 49). On the other hand, cleavage of SARS-S protein by TMPRSS2 promotes SARS-CoV-2 entering susceptible cells in an endosomal pathway independent manner, thus facilitating the virus to release fusion peptide for membrane fusion (50). Thereafter, cleavage of ACE2 increases the viral infectivity by about 30-folds, since the cleavage of SARS-CoV- 2 spike protein possesses higher furin score (0.688) when compared to SARS-CoV (0.139) (27, 51-53).

Immune system plays a pivotal role in the pathogenesis of COVID-19. During the preliminary stages of infection, SARS-CoV-2 activates the dendritic and epithelial cells, and triggers release of numerous pro-inflammatory cytokines and chemokines including IL-1β, IL-2, IL-6, IL-8, interferons (IFN-α/β), tumor necrosis factor (TNF), CeC motif chemokine 3 (CCL3), CCL5, CCL2, IP-10, etc. All these immune events collectively promote uncontrolled generation of these cytokines and chemokines referred to as cytokine storm, eventually leading to severe COVID-19 disease state (54-56).

4. ACE2 BASED STRATEGIES TO COMBAT COVID-19

The molecular mechanisms of COVID-19 pathogenesis in the gastrointestinal tract remain most elusive; however, several ACE2 based treatment strategies have been proposed. For example, ACE2 fusion proteins and TMPRSS2 inhibitors are recommended for rapid diagnosis or, treatment of COVID-19 (2). ACE2 inhibitors are also considered since GL1001 (selective ACE2 inhibitor) was demonstrated to reduce DSS-induced mucosal inflammation and distal colon pathology in inflammatory bowel disease (IBD) animal model (57). In addition, ACE2 inhibition is thought to elevate its substrate level which in turn would block over production of different pro-inflammatory cytokines (58). Noteworthy, SARS-CoV-2 is known to trigger cytokine storm, leading to multi-organ dysfunction in severe COVID-19 pneumonia patients (12). Based on these observations, it may be assumed that SARS-CoV-2 interacts with the gastrointestinal ACE2 receptor to increase mucosal membrane permeability, promoting generation of inflammatory cytokines and eventually leading to the destructive cytokine storm status (10). Thus, use of ACE2 inhibitors to reduce or inhibit SARS-CoV-2 induced gastrointestinal symptoms has future therapeutic relevance (10). The compounds which possess both anti-inflammatory and immunomodulatory properties seem to deliver positive effects in preventing GIT against such cytokine storm. In this regard, melatonin appears to be such a compound and its anti-inflammatory and immunomodulatory activities have been frequently reported in numerous animal and human studies (18, 59-62).

5. MELATONIN: A POTENTIAL REMEDY FOR COVID-19 ASSOCIATED GI PATHOLOGY

Melatonin can easily exert its actions on the targeting cells/organs since it is permeable to any cell or cell compartment due to its amphipathic nature. Moreover, presence of melatonin specific membrane transporters in the cell and mitochondrial membranes provides an advantage to move this molecule against its concentration gradient and accumulated in important organelles such as in mitochondria (63-64). The widely distributed melatonin receptors in diverse mammalian tissues, including the GIT, suggest its pleiotropic activities (21, 22, 65-67). Among these multiple activities, the antioxidant, anti-inflammatory and immunomodulatory effects have been well documented (21, 68-71). Even though lack of report on its direct viricidal action, the indirect anti-viral property of melatonin has been suggested (18). Several studies have shown that melatonin decreases the virus load (72), prevents oxidative stress mediated acute lung injury and inhibits unwanted immune response in mammals (18). The combination of melatonin's activities including potent antioxidant, anti-inflammatory, immunomodulatory and indirect anti-viral action are warranted to test therapeutic effects of this molecule on the digestive complications caused by SARS-CoV-2 infection.

5.1. Effects of melatonin in the gastrointestinal tract.

Identification of immunolocalization of melatonin in the enterochromaffin cells (EC) of mammalian digestive mucosa (73) and detection of the rate limiting enzymes of melatonin biosynthesis- arylalkylamine-*N*-acetyltransferase (AANAT) (21, 74-75) and hydroxyindole-O-methyltransferase (HIOMT) (76) confirm the synthesis of melatonin in the gastrointestinal tract of mammals. Further identification of melatonin specific membrane receptors and binding sites in the mammalian GIT uncovers the paracrine actions of melatonin (19, 77, 78). The locally synthesized melatonin primarily binds to its G-protein coupled membrane receptors- MT1 and MT2 to exert its paracrine activities while another receptor MT3 (human

quinone reductase 2) is also demonstrated to be involved in some actions of melatonin (79-80). Melatonin plays the critical roles under oxidative stress or inflammation receptor-independently or receptor-dependently to regulate intracellular signalling proteins, particularly antioxidant and pro-oxidant enzymes in GIT (66-67, 77, 79).

Being a well-known antioxidant, melatonin scavenges extremely toxic peroxynitrite anion, hydroxyl-, peroxynitrite-, peroxyyl radicals and singlet oxygen (81-83), thus it inhibits peroxidation of membrane lipids (84) and reduces the severity of inflammation (85, 86). Such direct antioxidant and free radical scavenging activities of melatonin are well examined in numerous *in vitro* and *in vivo* studies (85, 87, 88). Moreover, interaction of melatonin with reactive oxygen species (ROS) generates several metabolites which also have potent antioxidant property similar to melatonin (81, 86, 89). Notably, viral infections and their replication undergo spontaneous oxidation and provoke ROS formation Similarly, SARS-CoV-2 infection also causes generation of excessive ROS (14, 90). Thus, in the case of COVID-19 disease, melatonin is an ideal antioxidant to reduce the oxidative damage caused by SARS-CoV-2 infection.

5.2. Effects of melatonin on the microbiota of GIT and its association with covid-19.

Distribution of the normal microbial population in the GIT is essential to maintain the health and function of the intestine. Disturbance in such distribution and microbial signalling leads to gastrointestinal complications, known as "gut dysbiosis"- a phenomenon associated with numerous gastrointestinal diseases and disorders (91, 92). Similar to the gut micro environment, lungs also possess its own distinct microorganism population (93). Bacteroidetes and Firmicutes are abundant in the GIT, while they are also the predominating ones in the lungs (94). The gut microbes can modulate the pulmonary health through a bidirectional cross-talk termed as "gut-lung axis" (95). Under pathological condition, excessive endotoxins and microbial metabolites of gastrointestinal origin are released into the blood stream to cause inflammation in the lungs and vice-versa (96). It can be assumed that some gastrointestinal complications are caused by disruption of the gut micro environment after SARS-Cov2 infection. Gut microbes are reported to play a potent role in the pathogenesis of acute respiratory distress syndrome (ARDS) (97)- one of the major symptoms of SARS-Cov2 infection. On the other hand, the microbiota is responsible for the innate and adaptive immune responses of the GIT (98). In order to maintain the gut homeostasis, the pro-inflammatory and anti-inflammatory system must be balanced and such balance is performed by the commensal microorganisms (99). Usually, this homeostasis is disturbed by virus infections such as observed in the SARS-Cov2 invasion (100-103) and causes gastrointestinal symptoms in COVID-19 patients (101, 103-105).

In this context, melatonin is capable of maintaining the health of the intestine (106). Melatonin supplementation prevents the metabolic disturbances in varied animal studies possibly through re-establishment of the balance of beneficial microbiota in gut (107, 108). Melatonin also reduces gut membrane permeability and suppresses immune response initiated by *Escherichia coli* in gut (109). The importance of melatonin and its local production in the protection of GIT has been reported by Chojnacki *et al.* (110). They found that *Helicobacter pylori* infection downregulated the expression of *AANAT* and *HIOMT*, thus decreasing the endogenous synthesis of melatonin in the GIT while the melatonergic system was restored to normal after the infection abolishes. In light of the discussion, use of melatonin may help to rebuild the disturbed GIT microtia caused by SARS-Cov2 infection and improve the GI symptoms in COVID-19 patients.

5.3. Anti-inflammatory and immuno-modulatory properties of melatonin: an armament against covid-19 induced gastrointestinal complications.

Accompanied with its antioxidant property, melatonin also possesses potent anti-inflammatory and immunomodulatory actions in diverse mammalian tissues, particularly in the gastrointestinal tract (18, 21, 69, 111-113). For example, transcription factor, NF-kβ is extremely sensitive to oxidative stress and under this stress it triggers expression of different pro-inflammatory genes and increases the state of inflammation in cells (69, 114). By suppressing oxidative stress melatonin overcomes inflammatory response primarily via modulation of NF-kβ associated signalling pathways involving TLR4 and TLR5 (68-69, 115). Melatonin downregulates the expression of *TLR4* and other genes associated with its signalling cascade including *MyD88* (116). In most of the cases, melatonin inhibits *NF-kβ* expression by increasing Ikβ level which suppresses the excessive production of adhesive agents, leukocytes and other inflammatory cells (117), ultimately restricting the level of inflammatory reactions in the GI tissue. Similarly, melatonin also inhibits the level of proinflammatory cytokine IL-1β in aflatoxin B1 induced rat intestinal lesions (118). Mast cells are important innate immune cells in GIT and abundance of melatonin receptors are present in these cells. By acting on these receptors, melatonin restricts the release of TNF-α from mast cells (119) and inhibits the activation of mast cells by down-regulating the expression of the NF-κB to exert its anti-inflammatory and immunoregulatory activities (120). The other anti-inflammatory pathways of melatonin include inhibition of the production of prostaglandins and adhesion molecules (85), restricting leukocyte transendothelial cell migration (121), cyclooxygenase 2 expression in the macrophages (122) and inhibiting the recruitment of various pro-inflammatory cells to the inflammation site (85, 123). Interestingly, AFMK and AMK- the metabolites of melatonin also play potent anti-inflammatory actions as does melatonin (123).

It is noted that the overreaction of the innate immune responses and excessive inflammatory reaction are the major risk factors associated to the severity and mortality of COVID-19 patients (9-11, 14, 71, 124-126). This provides the rationality behind the use of melatonin in preventing and treating gastrointestinal complications caused by such overreaction of the innate immune response and excessive inflammatory reaction in COVID-19 patients. As mentioned earlier, SARS-CoV-2 triggers the dendritic cells and epithelial cells to release pro-inflammatory cytokines and chemokines (Figure 1) creating a destructive cytokine storm and eventually increasing the disease severity (54-56). A profound reduction in the circulating levels of neutrophils and lymphocytes was also noticed in COVID-19 patients (10, 127). Although endoscopic studies did not reveal any macroscopic inflammation in the GIT, but numerous infiltrating plasma cells and lymphocytes with interstitial oedema were noted in the lamina propria of the stomach, duodenum and rectum of a COVID-19 patient clearly suggesting an activation of mucosal immune cells (128). Further study on the inflammatory markers in affected patients indicated profound increase in their circulatory levels of procalcitonin, C reactive protein, D-dimer and ferritin (5,124); and TNF, IL-2R, IL-6, IL-8 and IL-10 levels were also elevated in the serum of patients with severe infection, but levels of IL-1β and interferon-gamma producing CD4+ and CD8+ T cells were not affected (128). However, plasma levels of IL-1beta, IL-1ra, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-17, fibroblast growth factor, granulocyte colony-stimulating factor, granulocyte macrophage-colony stimulating factor, interferon-gamma, TNF, vascular endothelial growth factor, IP-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1alpha, platelet-derived growth factor and MIP-1beta were distinctly increased in ICU patients. Collectively, the over responses of the immune cells to SARS-CoV-2 invasion caused cytokine storm syndrome in COVID-19 patients (1, 125).

The evidence mentioned above suggests the importance of the innate immune system in GIT for SARS-CoV-2 infection. In the GIT, intestinal mucosa serves as the primary defensive layer against intruded pathogens. Apart from its basic absorptive enterocytes, goblet cells, enteroendocrine cells, and Paneth cells, the underlying lamina propria exclusively comprises of the immunocompetent cells that are responsible for the innate immune response in the mucosa (126). Pathogens often bind to pathogen-recognition receptors (PRRs), most often the TLRs, localized on the cell surface or endosomes of the intestinal epithelial cells and other immunocompetent cells in the lamina propria to initiate innate immune responses (126). Other PRRs including Nucleotide-binding oligomerization domain (NOD) (129-130) and nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs) (131-132) are also responsible for pathogen innate immune responses and inflammation. NLPR3 inflammasome represents the most common inflammatory reaction involving ASC, caspase-1, a pro-IL-1β and pro-IL-18 to form mature and secreted interleukins (126). Gut-associated lymphoid tissue (GALT) regulates IgA production and its release from the intestinal B cells into the lumen to maintain the intestinal homeostasis (126). Paneth cells, the prime source of antimicrobial proteins, synthesize and secrete lysozyme, secretory phospholipase A2, C-lectin RegIIIγ, α-defensins and angiogenin-4 to clean the pathogen (126). All these innate immune responses can be activated by SARS-Cov-2 infection and the uncontrolled innate immune responses often occur in the severe COVID-19 patients with intestinal symptoms (2, 14, 133). The capability of SARS-CoV to deplete mucosal lymphoid tissue in the pharynx, appendix, and small intestines has been reported in humans (134) and the similar reactions are expected to occur also in SARS-CoV-2 infection. The SARS-CoV positive *in situ* hybridization signals were also identified in the cytoplasm of mucosal epithelial cells (135, 136) as well as in mucosal and submucosal lymphocytes (136). Electron microscopic studies revealed the abundance of viral particles in the mucosal epithelial cells, particularly in the dilated endoplasmic reticulum and surface of the microvilli (136-137). Viral proteins and genomic sequences were also detected in the gastric parietal cells (138).

Melatonin seems to be of utmost importance to control the unbalanced innate immune response in GIT induced by SARS-CoV-2 infection. Animal studies have unveiled the potent roles of melatonin in the regulation of the immune response under inflammatory states in the bone marrow and other tissues where the proliferation and maturation of the lymphocytes (both T and B), NK cells, granulocytes and monocytes occur (139). Furthermore, melatonin treatment improves antigen presentation in macrophages possibly through induction of complement receptor 3, MHC class I and class II, and CD4 antigens (140). Melatonin treatment also downregulates the circulating levels of different proinflammatory interleukins (IL-1β, IL-6, IL-17), interferon-γ, TNF-α, kinase Cζ (PKCζ) and calmodulin 3 (CALM3) (66, 141-143). The damages in the colonic mucosa and other parts of the GIT related to autoimmune response, inflammation and sepsis are significantly reduced with melatonin treatment (144, 145). Clinical trials also show that melatonin supplementation reduces the circulating levels of TNF-α and IL-6 of patients (146). In acute lung injury, similar to found in COVID-19 disease, the anti-inflammatory and immunomodulatory actions of melatonin play important roles to protect against this injury (15) (Figure 1). Thus, melatonin is a potent compound with antioxidant, anti-inflammatory and immunomodulatory properties- the three essential characteristics in a single compound to combat COVID-19 induced digestive disorders.
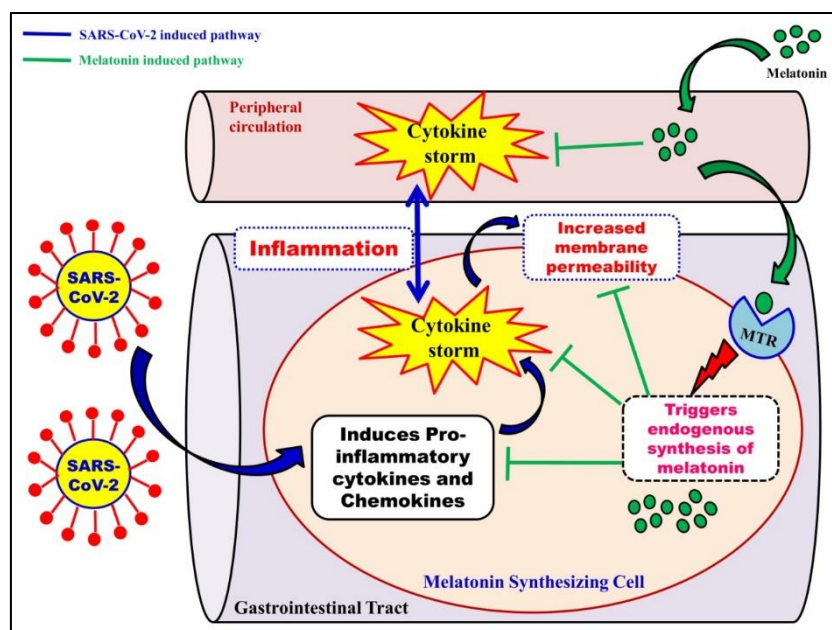
Fig. 1. Hypothetical model of the protective role of melatonin against SARS-CoV-2 induced gastrointestinal inflammation.
Blue lines indicate SARS-CoV-2 induced inflammatory pathways, while green lines indicate melatonin mediated pathways of protection. MTR- Melatonin receptor; SARS-CoV-2- severe acute respiratory syndrome coronavirus 2.

6. FUTURE PERSPECTIVES

Finally, it is essential to know about the safety measures of this molecule. In this regard, melatonin is ideal since its short-term and long-term use in human, even in ICU patients, reported no serious adverse effects (147-149). Similarly, melatonin at higher dose (1 g/day) for prolonged period use in human, or in acute lung injury animal models has not shown any adverse effect (17, 18, 150, 151). Since the effect of melatonin has not been tested in COVID-19 patient in a large scale, verification of the therapeutic effects of melatonin in COVID-19 patients is recommended (133). Melatonin has the capacity to inhibit exaggerated cytokine storm in the infected individuals, thus it can restrict the severity of COVID-19 disease (152, 153), particularly in the gastrointestinal tract. Collectively, in light of these evidences it is likely that melatonin has the positive effects on digestive complications in COVID-19 patients. Its beneficial effects may be superior to other contemporary antioxidant molecules. However, such hypothesis is worth with the extensive clinical trials in the future.

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AUTHORSHIP

Prof. DB contributed to conception, revised the manuscript and approved it, Dr. AC critically read and revised the manuscript and approved it. Dr. PKP also contributed to conception, prepared figures, drafted the manuscript and incorporated corrections into the manuscript as and when required.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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