Sarcouncil Journal of Internal Medicine and Public Health

ISSN(Online): 2945-3674

Volume- 01| Issue- 01| 2022

Review Article **Received:** 05-03-2022 | **Accepted:** 15-03-2022 | **Published:** 21-03-2022

Implication of Melatonin against COVID-19 Mediated Gastrointestinal Symptoms: An Overview

Palash Kumar Pal*[1] *and Ashis Kumar Panigrahi*[2]*

[1]*Department of Physiology, University of Calcutta, 92, A.P.C. Road, Kolkata-700009, India*

[2]*Pro-Vice Chancellor, The University of Burdwan, West Bengal- 713104, India.*

Abstract: Emergence of a sudden novel coronavirus disease (COVID-19), reported primarily in the Wuhan, Hubei province of China, changed the scenario of global medical science. Observing the increasing human loss and seriousness of the situation, World Health Organization (WHO) declared it as a global pandemic in March 2020. However, later it was defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses defined. In earlier stages of infection, COVID-19 was demonstrated as a lethal lung disease, but increasing reports regarding gastrointestinal (GI) complications clearly suggested GI tract as a possible route of SARS-CoV-2 infection and at the same time also indicated that SARS-CoV-2 in not confined to lungs only and may migrate to other vital organs. Further research revealed that SARS-CoV-2 pathogenesis primarily through upregulation of different chemokines and interleukins, a situation termed as "cytokine storm". In this regard, melatonin, an endogenous indolamine hormone, seems to be the most promising therapeutic agent to neutralize SARS-CoV-2 induced pathological states. Being a powerful antioxidant, immunomodulator and anti-inflammatory agent, implication of melatonin against COVID-19 induced GI complications cannot be neglected. Moreover, existence of the endogenous synthesizing machinery of melatonin distributed throughout the entire length of the GI tract adds on to its advantages over other therapeutic molecules. Despite of the fact that melatonin is reported to have no serious side effect at short- or long term use and even at high dose, but its implacability must undergo standard medical protocols before being applied to human beings.

Keywords: COVID-19; Gastrointestinal symptoms; SARS-CoV-2; Melatonin; Antioxidant.

INTRODUCTION

In early 2019, detection of complicated pneumonia caused by novel coronaviride virus family member, coronavirus, in Wuhan, Hubei province of China got finally defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020 by International Committee on Taxonomy of Viruses (ICTV) (Gu. *et al.*, 2020; Ng and Tilg, 2020; Phelan. *et al.*, 2020; Wu. *et al.*, 2020; Zhu. *et al.*, 2020). On 11th March, 2020, World Health Organization (WHO) designated SARS-CoV-2 infection as pandemic due to its pleiotropic transmission modes causing enormous loss of human life globally (Gu. *et al.*, 2020). Existence of non-segmented positive sense RNA in the virus envelope and its distribution in multiple mammalian species facilitates such beta coronavirus to develop complex respiratory syndromes (Kuiken. *et al.*, 2003; Su. *et al.*, 2016; Huang. *et al.*, 2020). On 27th January, 2022 WHO has declared 364,191,494 numbers of COVID-19 cases and 5,631,457 deaths in their global situation report. Apart from the respiratory symptoms and complications (Chen. *et al.*, 2020; Huang. *et al.*, 2020), about 10% COVID-19 patients were also found to face severe diarrhea along with abdominal pain and vomiting. Such contention indicated the possible involvement of the gastrointestinal tract in the development of SARS-CoV-2 infection. As mentioned by WHO on 26th November 2021, five different variants of SARS-CoV-2 have been spotted in different parts of the world of which Omicron has been evidenced for serious concern due to its rapid transmission and potentially of re-infection. Despite of the numerous attempts to understand the underlying mechanism of SARS-CoV-2 infection in the gastrointestinal tract (GIT) and its spread to the other organs, only spoon full information has been gathered (Leung. *et al.*, 2020; Zhang. *et al.*, 2020).

On the other hand, melatonin (N-acetyl-5-methoxytryptamine), an endogenous hormone is known for its pleiotropic beneficial actions in treating diverse diseases and pathological states in mammals induced by varied modes. Notably, this tiny indolamine is also well demonstrated to be advantageous in combat against different respiratory associated diseases and viral infections (Huang. *et al.*, 2010; Yip. *et al.*, 2013; Wu. *et al.*, 2019; Reiter. *et al.*, 2020). Moreover, availability of melatonin receptors and evidence regarding the presence of its endogenous synthesis throughout the GIT of diverse mammal, including human (Kvetnoy. *et al.*, 2002; Pal. *et al.*, 2018), promoted its local actions as a strong anti-inflammatory, immunomodulatory and antioxidative agent. Based on the available evidences, implication of melatonin in restricting SARS-CoV-2 persuaded respiratory complications and other side effects cannot be overlooked (Pal. *et al.*, 2018, 2019; Reiter. *et al.*, 2020). Thus, novelty of this present treatise lies in its hypothesis indicating the utility

***Corresponding Author:** Ashis Kumar Panigrahi

of endogenous as well as exogenous melatonin as a potent agent in restricting or, curing SARS-CoV-2 induced GI complications. However, detailed research on this area is required in future before its application in any human being.

COVID-19 Respiratory Disease and Gastrointestinal Tract: A *VIS-A-VIS* Relationship

Depending on the clinical data gather so far, it is clear that SARS-CoV-2 infection is not solely lung associated phenomena, it may also be transmitted to other important mammalian organs where it may cause serious injury to the tissue or organ (Hu. *et al.,* 2020; Yang. *et al.*, 2020; Yao. *et al.*, 2020). Such contention earns support as coronavirus family members, in general, are reported to affect the respiratory system, GI tract and central nervous system in human and other mammalian species (Perlman and Netland, 2009). Since, anorexia and diarrhoea were common digestive symptoms in SARS-CoV-2 positive patients therefore GI tract is suggested as a prime target organ for Covid-19 infection (Leung. *et al.*, 2020; Lu. *et al.*, 2020; Mao. *et al.*, 2020; Ng and Tilg, 2020).

Variants of Sars-CoV-2

Based on the enhanced risk to public health, WHO in late 2020 defined the different emerging variants of SARS-CoV-2 in two categorise- Variants of Interest (VOIs) and Variants of Concern (VOCs) to track the pandemic situation and ongoing development in research. Meanwhile, WHO has designated five different variants of SARS-CoV-2 reported at different regions of the world during different time-

Alpha variant (B.1.1.7; Pango lineage) that possess additional amino acid changes at location +S:484K and +S:452R was first reported in the United Kingdom during September 2020, and got finally designated on 18th December, 2020;

Beta variant (B.1.351; Pango lineage) that possess additional amino acid changes at location +S:L18F was first reported in South Africa during May 2020, and got finally designated on 18th December, 2020;

Gamma variant (P.1; Pango lineage) that possess additional amino acid changes at location +S:681H was first reported in Brazil during November 2020, and got finally designated on 11th January, 2021;

Delta variant (B.1.617.2; Pango lineage) that possess additional amino acid changes at location +S:417N and +S:484K was first reported in India during October 2020. The VOI and VOC were designated on 4th April, 2021 and 11th May, 2021, respectively; and

Omicron variant (B.1.1.529; Pango lineage) that possess additional amino acid changes at location +S:R346K was first reported in multiple countries during November 2021. The VOI and VOC were designated on 24th November, 2021 and 26th November, 2021, respectively. Among these different variants of SARS-CoV-2, omicron seems to be of present concern because of its unique potentiality to undergo rapid and prolong mutation that enhances it probability to re-infect people.

SARS-CoV-2 and Gi Tract: The Hypothesis

Microbial infection in the mammalian GI tract is restricted due to the presence of immune-regulatory intestinal epithelial barrier (Harvey. *et al.*, 2017). Generally, viruses especially corona virus infects and damages the absorptive enterocyte leading to insufficient absorption and abnormal intestinal secretion that eventually triggers enteric nervous system (Desmarets. *et al.*, 2014; Ettayebi. *et al.*, 2016; Crawford. *et al.*, 2017). Interestingly, SARS-CoV-2 infection was reported in different parts of the GI tract in 2 corona positive patients and in the stool samples of about 22 patients (Holshue. *et al.*, 2020; Mao. *et al.*, 2020; Ng and Tilg, 2020; Tang. *et al.*, 2020; Xie. *et al.*, 2020). Thus, viral growth in the intestinal cells proves the susceptibility of the GI tract to SARS-CoV-2 infection where the virus infects two particular type of cells viz. oesophageal upper cells and absorptive enterocytes that possess receptors for angiotensin converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). This may be the possible cause behind the emergence of diarrhoea and nausea 1-2 days before the development of fever along with respiratory symptoms (Pan. *et al.*, 2020; Wang. *et al.*, 2020; Zhang. *et al.*, 2020). Evidences demonstrated the capability of SARS-CoV-2 in damaging human liver though their association with ACE2 receptors causing their over-expression in the hepatic cells (Guan. *et al.*, 2020). Similarly, SARS-CoV-2 is also found to modulate intestinal microflora which in turn alters mucosal immune strategies, thus affecting the respiratory tract (Budden. *et al.*, 2017; He. *et al.*, 2017). In light of these evidences, it is clear that emergence of frequent GI complications and increasing disease severity in COVID-19 patients

Publisher: SARC Publisher

may result from increasing viral replication in the resident GI cells (Pan. *et al.,* 2020).

SARS-CoV-2: Entry and Pathogenesis in Gastrointestinal Tract

In case of transmission between human, people in close proximity (1 meter) are at high risk of getting infected to SARS-CoV-2, since direct contact or air droplets serve as the prime mediators in such transmission (Gu. *et al.,* 2020; Wang. *et al.,* 2020; Zhu. *et al.,* 2020). Although a few fragmentary reports are available on the mode of SARS-CoV-2 infection in the GI tract, but the exact mechanism is still not revealed. Recent research on single-cell RNA sequencing have revealed that SARS-CoV-2 virus, in order to enter the gastrointestinal host cell, targets only those intestinal cells that expresses both receptors of ACE2 and TMPRSS2 (Chai. *et al.,* 2020; Liang. *et al.,* 2020; Zhang. *et al.,* 2020; Zhou. *et al.,* 2020). Such contention earns support since increased ACE2 and TMPRSS2 expression was noted in different GI samples of SARS-CoV-2 infected persons (Liang. *et al.,* 2020; Zhang. *et al.,* 2020; Zhou. *et al.,* 2020). Such novel observation supported the capability of SARS-CoV-2 to spread to other extrapulmonary organs or, tissues (Chai. *et al.,* 2020; Zhang. *et al.,* 2020) possibly through enhanced permeability to intestinal lipopolysaccharide (Powers. *et al.,* 2020).

Based on the data gathered so far, it is clear that transmission and pathogenesis of SARS-CoV-2 involves multiple steps- (i) SARS-CoV-2 attaches to the host cell and recognizes specific surface receptor; (ii) Protease cleaves and fuses membranes; (iii) Transmembrane spike glycoprotein (S-protein) of SARS-CoV-2 recognizes the binding domains and binds to ACE2 and TMPRSS receptors; and (iv) Enters the host cell, starts replication and increases viral load, thus enhances the disease severity (Huang. *et al.,* 2020). Notably, CTD1 possess a predetermined receptor-binding domain for ACE2, binding to which enhances the virulence and spread of SARS-CoV (Li. *et al.,* 2005; Gui. *et al.,* 2017). In order to promote binding to ACE2, CTD1 undergoes conformational changes by regulating its interaction with CTD2, S1-ACE2 complex and the S2 subunit (Song. *et al.,* 2018). In case of binding affinity to ACE2, SARS-CoV-2 S protein was found to be superior to SARS CoV S protein (Wang. *et al.,* 2020; Wrapp. *et al.,* 2020; Xu. *et al.,* 2020). The entry of SARS-CoV-2 in the susceptible cell occurs without involving the endosomal pathway and such pathway is triggered as soon as TMPRSS2 cleaves SARS-S protein. As a result membranes get fused with the help of fusion peptide released by the virus (Hoffmann. *et al.,* 2020). In immunity perspective view, dendritic and epithelial cells along with different pro-inflammatory cytokines and chemokines are reported to be turned on during the earlier stages of SARS-CoV-2 infection. Such sudden increase of these cytokines in critical SARS-CoV-2 patients is termed as "cytokine storm" (Figure 1) that ultimately was found to promote the progression of COVID-19 pathogenesis in the infected patients (Cheung. *et al.,* 2005; Chu. *et al.,* 2016; Huang. *et al.,* 2020). Several strategies were adopted immediately to restrict or, overcome the issues where ACE2 was selected as a potent therapeutic target (Gu. *et al.,* 2020) but were not successful as expected. Since oxidative stress and immune system associated molecules were suggested to be the prime cues involved in the development of SARS-CoV-2 pathogenesis in the GI tract; therefore implication of a certain endogenous molecule, that may serve as both anti-inflammatory and immunomodulatory agent, could have been beneficial. In such regards, as evident from numerous mammalian studies, an endogenous indolamine hormone known as melatonin may be advantageous to other competitors because of its potent anti-inflammatory and immunomodulatory actions (Hardeland, 2018; Reiter. *et al.,* 2020).

Publisher: SARC Publisher

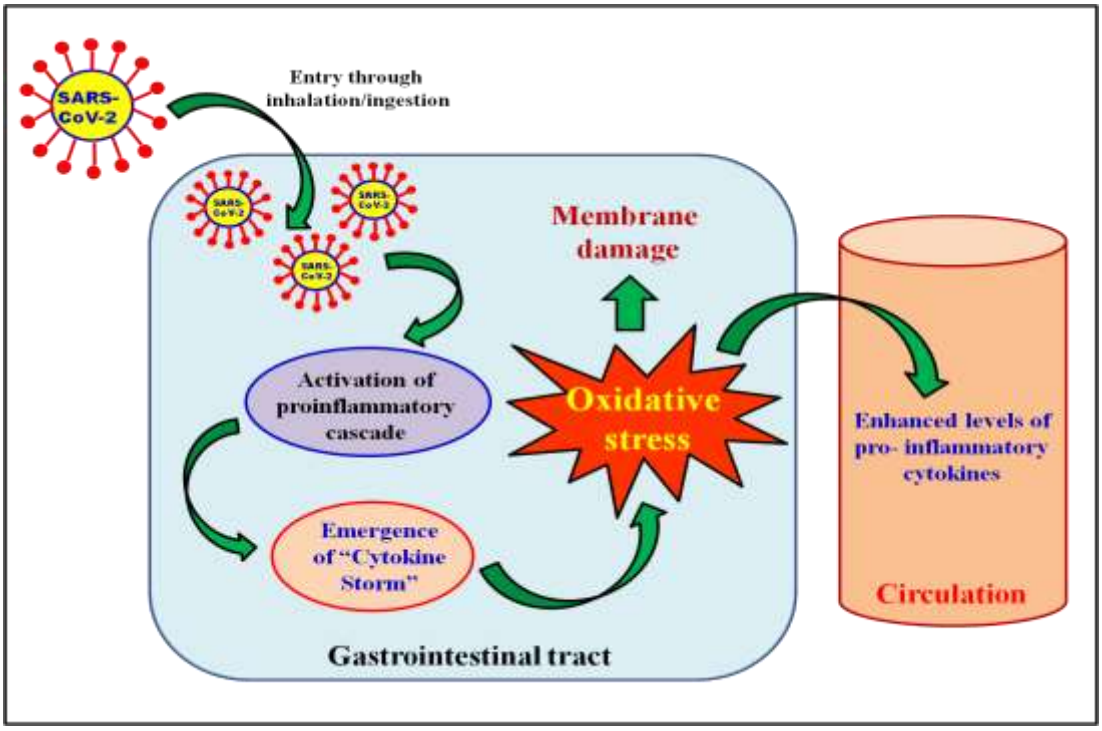

Figure 1: Diagrammatic representation of entry and pathogenesis of SARS-CoV-2 in the gastrointestinal tract

Why Melatonin?

Being an amphiphilic molecule, melatonin (*N*-acetyl-5-methoxy tryptamine) can travel through any biological membrane during which specific membrane transporters present in different cells/tissues and mitochondria promotes its movement beyond the concentration gradient, thus becomes concentrated in different cellular organelles (Tan. *et al.*, 2016; Mayo. *et al.*, 2018). Moreover, existence of melatonin specific receptors in multiple mammalian cells/tissue including the entire length of the GI tract suggested its diverse modes of actions (Rodriguez. *et al.*, 2004; Pal. *et al.*, 2018, 2019; Pal and Maitra, 2018). Although direct viricidal property of melatonin is yet not established but keeping the involvement of cytokine storm and oxidative stress in SARS-CoV-2 pathogenesis in mind, melatonin seems to be advantageous due to its direct and indirect antioxidant, anti-inflammatory and immunomodulatory properties (Cuzzocrea and Reiter, 2001; Mauriz. *et al.*, 2013; Pal. *et al.*, 2018; Mitra. *et al.*, 2019; Tan and Hardeland, 2020). Since, melatonin treatment was reported to decrease virus load during acute lung injury (Ben-Nathan. *et al.*, 1995; Reiter. *et al.*, 2020), therefore possibility remains regarding the indirect anti-viral role of melatonin against SARS-CoV-2 infection (Reiter. *et al.*, 2020); however such hypothesis needs to be tested through carefully designed detailed investigation.

Existence and Function Relevance of Melatonin in Gastrointestinal Tract

Melatonin was first immunohistochemically localized in the enterocromaffin cells of the mucosal lining of mammalian GI tract (Raikhlin and Kvetnoy, 1974). Later, identification of arylalkylamine-*N*-acetyltransferase (AANAT) (Fu. *et al.*, 2001; Slominski. *et al.*, 2008; Pal. *et al.*, 2018) and hydroxyindole-O-methyltransferase (HIOMT) (Hong and Pang, 1995) confirmed the endogenous synthesis of melatonin in the mammalian GI tissue. The paracrine actions of melatonin were supported by the presence of its membrane bound specific receptors and binding sites where melatonin of gastrointestinal origin was also suggested to contribute in the peripheral circulation (Brzozowski. *et al.*, 1997; Dobocovich and Mankowsha, 2005). Melatonin was reported to exert its actions on the target cells through 3 specific receptors- MT1, MT2 and MT3 (human quinone reductase 2) (Witt-Enderby. *et al.*, 2006; Srinivasan. *et al.*, 2012). Under elevated oxidative load, melatonin regulates the antioxidant defence system by activating or deactivating these receptors to restore the intracellular level of free radicals (Rodriguez. *et al.*, 2004).

Due to the potent receptor independent antioxidant property, melatonin quenches diverse free radicals directly, thus inhibiting the membrane lipids from undergoing unwanted peroxidation process and restricts the progression of inflammatory cascades

Publisher: SARC Publisher

(Cuzzocrea and Reiter, 2002; Tan. *et al.*, 2002; Reiter. *et al.*, 2001, 2016; Torres-Farfan. *et al.*, 2003; Saito. *et al.*, 2005; Tan and Reiter, 2019). Even the metabolites resulting from the interaction of melatonin and different reactive oxygen species also serve as strong antioxidants under oxidative stress conditions (Tan. *et al.*, 2002; Lopez-Burillo. *et al.*, 2003; Nosál'ová. *et al.*, 2007). Notably, SARS-CoV-2 pathogenesis in evident as a resultant of rapid and uncontrolled viral duplication during which enormous amount of free radicals are generated within the cell/tissue that promotes the inflammatory pathways and disease symptoms arises (Imai. *et al.*, 2008; Zhang. *et al.*, 2020). In this context, implication of melatonin as a therapeutic agent to neutralize the overproduction of free radicals and reactive oxygen species to inhibit disease progression cannot be neglected.

Implication of Melatonin in Sars-Cov-2 Induced Gi Symptoms

Among the mammalian tissues investigated so far, efficacy of melatonin as a potent antioxidant, anti-inflammatory and immunomodulatory agent has been documented mostly in the gastrointestinal tract (Galano. *et al.*, 2011; Carrillo-Vico. *et al.*, 2013; Mauriz. *et al.*, 2013; Dong. *et al.*, 2016; Pal. *et al.*, 2018; Reiter. *et al.*, 2020). On the other hand, transcription factor particularly NF-kβ reacts extremely well to oxidative stress which in turn activates diverse pro-inflammatory genes that ultimately promotes intra-cellular inflammatory state (Reiter. *et al.*, 2000; Mauriz. *et al.*, 2013).

In most of the cases, melatonin has been documented to exert its anti-inflammatory actions through regulation of these NF-kβ mediated signalling cascades (Cuzzocrea. *et al.*, 2001; Mauriz. *et al.*, 2013; Vriend and Reiter, 2014). In contrast, patients with SARS-CoV-2 infection revealed declining levels of lymphocyte, neutrophil and CD8+ T cells in the peripheral circulation possibly due to induction of cytokine storm that results from cumulative responses of diverse interleukins and interferons (Chen. *et al.*, 2020; Liu. *et al.*, 2020). In this context, melatonin may fit appropriate as a therapeutic agent to restrict the development of such cytokine storm particularly in the GI tract. Under inflammatory condition, exogenous melatonin is demonstrated to enhance lymphocyte count, natural killer cells, granulocytes and monocytes by triggering their proliferation and maturation processes, thus helps in overcoming the pathological state (Miller. *et al.*, 2006). Moreover, melatonin enhances the expression of different complement system associated components such as complement receptor 3, MHC class I and class II, and CD4 antigens to help macrophages in presenting specific antigens (Kaur and Ling, 1999). At the same time, application or, supplementation of melatonin is reported to decline the expression of circulatory levels of different cytokines and chemokines that includes interferon-γ, calmodulin 3, interleukins (IL-1β, IL-6, IL-17), TNF-α and kinase Cζ (PKCζ) (Mauriz. *et al.*, 2013; Park. *et al.*, 2015; Sanchez-Lopez. *et al.*, 2018; Bazyar. *et al.*, 2019; Zarezadeh. *et al.*, 2019). Such observations clearly suggested the potentiality of melatonin to recover colonic mucosa and other gastrointestinal portions from diverse modes of injuries (Tahan. *et al.*, 2011; Volt. *et al.*, 2016). In addition to the beneficial roles of melatonin in the GI tract, its anti-inflammatory and immunomodulatory properties have also been reported against acute lung injury (Huang. *et al.*, 2010), a situation similar to that of SARS-CoV-2 infection. Collectively, it appears that existence of the three prime properties viz. antioxidant, immunomodulation and anti-inflammation, required to combat against SARS-CoV-2 infection mediated GI complications, makes it the most advantageous agent in comparison to other therapeutic molecules.

Precautions and Future Perspectives

In order to apply melatonin in SARS-CoV-2 infected patients, its pharmacological aspects must be kept in mind as determined in case of other therapeutic agents. Interestingly, numerous studies have ascertained that melatonin possess no serious side effects, neither when used for short- or, long-terms nor, at relatively higher dose (1 g/day) even in critical patients and acute lung injury animal models (Nordlund and Lerner, 1977; Bourne. *et al.*, 2008; Mistraletti. *et al.*, 2015; Sun. *et al.*, 2015; Andersen. *et al.*, 2016; Wu. *et al.*, 2019; Reiter. *et al.*, 2020). However, the effects of use of melatonin against this specific SARS-CoV-2 has never been reported and thus must undergo common medical protocols before being applied to human beings. Since, cytokine storm seems to be the culprit in progression of SARS-CoV-2 pathogenesis in the GI tract therefore utility of melatonin to restrict such infection cannot be neglected, although such hypothesis required detailed investigation in the coming days.

Publisher: SARC Publisher

ACKNOWLEDGEMENTS

Dr. Palash Kumar Pal gratefully acknowledges the receipt of UGC Dr. D. S. Kothari Post Doctoral Fellowship (BL/16-17/0502), Govt. of India.

REFERENCES

1. Andersen, L.P.H., Gogenur, I., Rosenberg, J. & Reiter, R.J. "The safety of melatonin in humans." *Clinical drug investigation* 36.3 (2016): 169–175.
2. Bazyar, H., Gholinezhad, H., Moradi, L., Salehi, P., Abadi, F., Ravanbakhsh, M. & Javid, A.Z. "The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: a double-blind, placebo-controlled trial." *Inflammopharmacology* 27.1 (2019): 67-76.
3. Ben-Nathan, D., Maestroni, G.J., Lustig, S. & Conti, A. "Protective effects of melatonin in mice infected with encephalitis viruses." *Arch. Virol.* 140 (1995): 223–230.
4. Bourne, R.S., Mills, G.H. & Minelli, C. "Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial." *Crit. Care (London, England)*. 12 (2008): R52.
5. Brzozowski, T., Konturek, P.C., Konturek, S.J., Pajdo, R., Bielanski, W., Brzozowska, I., Stachura, J. & Han, E.G. "The role of melatonin and L-tryptophan in prevention of acute gastric lesions induced by stress, ethanol, ischemia, and aspirin." *J. Pineal Res.* 23 (1997): 79-89.
6. Bubenik, G. A. "Localization and physiological significance of gastrointestinal melatonin. In: R Watson (ed.) Melatonin in Health Promotion." *CRC press, Boca Raton, Florida* (1999); 21–39.
7. Budden, K.F., Gellatly, S.L., Wood, D.L., Cooper, M.A., Morrison, M., Hugenholtz, P. & Hansbro, P.M. "Emerging pathogenic links between microbiota and the gut-lung axis." *Nat. Rev. Microbiol.* 15 (2017): 55-63.
8. Carrillo-Vico, A., Lardone, P.J., Alvarez-Sánchez, N., Rodríguez-Rodríguez, A. & Guerrero, J.M. "Melatonin: buffering the immune system." *Int. J. Mol. Sci.*14 (2013): 8638–8683.
9. Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., *et al*. "Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection." *BioRxiv*. (2020).
10. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X. & Zhang, L. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study." *Lancet.* 395 (2020): 507-513.
11. Cheung, C.Y., Poon, L.L.M., Ng, I.H.Y., Luk, W., Sia, S.F., Wu, M.H.S., Chan, K.H., Yuen, Y., Gordon, S., Guan, Y. & Peiris, J.S.M. "Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages *in vitro*: possible relevance to pathogenesis." *J. Virol.* (2005) 797819–797826.
12. Chu, H., Zhou, J., Wong, B.H.Y., Li, C.C., Chan, J.F.W., Cheng, Z.S., Yang, D., Wang, D., Lee, A.C.Y., Li, C.C., Yeung, M.L., Cai, J.P., Chan, I.H.Y., Ho, W.K., To, K.K.W., Zheng, B.J., Yao, Y., Qin, C. & Yeun, K.Y. "Middle east respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways." *J. Infect. Dis.* 213 (2016): 904–914.
13. Crawford, S.E., Ramani, S., Tate, J.E., Parashar, U.D., Svensson, L., Hagbom, M., Franco, M.A., Greenberg, H.B., O'Ryan, M., Kang, G., Desselberger, U. & Estes, M.K. "Rotavirus infection." *Nat. Rev. Dis. Primers.* 3 (2017): 17083.
14. Cuzzocrea, S. & Reiter, J.R. "Pharmacological action of melatonin in acute and chronic inflammation." *Curr. Top. Med. Chem.* 2 (2002): 153–165.
15. Cuzzocrea, S. & Reiter, R.J. "Pharmacological action of melatonin in shock, inflammation and ischemia/reperfusion injury." *Eur. J. Pharmacol.* 426 (2001): 1–10.
16. Desmarets, L.M.B., Theuns, S., Roukaerts, I.D.M., Acar, D.D. & Nauwynck, H.J. "Role of sialic acids in feline enteric coronavirus infections." *J. Gen. Virol.* 95 (2014): 1911–1918.
17. Dobocovich, M. & Mankowsha, M. "Functional MP1 and MP2 melatonin receptors in mammals." *Endocrine.* 27 (2005): 101–110.
18. Dong, Y., Fan, C., Hu, W., Jiang, S., Ma, Z., Yan, X., Deng, C., Di, S., Xin, Z., Wu, G., Yang, Y., Reiter, R.J. & Liang, G. "Melatonin attenuated early brain injury induced by subarachnoid hemorrhage via regulating NLRP3 inflammasome and apoptosis signalling." *J. Pineal Res.* 60 (2016): 253–262.
19. Ettayebi, K., Crawford, S.E., Murakami, K., Broughman, J.R., Karandikar, U., Tenge, V.R.,

Publisher: SARC Publisher

et al. "Replication of human noroviruses in stem cell-derived human enteroids." *Science*. 353 (2016): 1387–1393.
20. Fu, Z., Kato, H., Kotera, N., Noguchi, T., Sugahara, K. & Kubo, T. "Regulation of hydroxyindole-O-methyltransferase gene expression in Japanese quail (*Coturnixcoturnix japonica*)." *Biosci. Biotechnol. Biochem.* 65 (2001): 2504–2511.
21. Galano, A., Tan, D.X. & Reiter, R.J. "Melatonin as a natural ally against oxidative stress: a physicochemical examination." *J. Pineal Res.* 51 (2011): 1–16.
22. Gu, J., Han, B. & Wang, J. "COVID-19: gastrointestinal manifestations and potential fecal-oral transmission." *Gastroenterology*. (2020) S0016-5085(20)30281-X.
23. Guan, W., Ni, Z., Hu, Y., *et al*. "Clinical characteristics of coronavirus disease 2019 in China." *N. Engl. J. Med.* 382 (2020): 1708-1720.
24. Gui, M., Song, W., Zhou, H., Xu, J., Chen, S., Xiang, Y. & Wang, X. "Cryo- electron microscopy structures of the SARS–coV spike glycoprotein reveal a prerequisite conformational state for receptor binding." *Cell Res.* 27 (2017): 119–129.
25. Haber, A.L., Biton, M., Rogel, N., Herbst, R.H., Shekhar, K., Smillie, C., *et al*. "A single-cell survey of the small intestinal epithelium." *Nature*. 551 (2017): 333-339.
26. Hardeland, R. "Review Melatonin and retinoid orphan receptors: Demand for new interpretations after their exclusion as nuclear melatonin receptors." *Melatonin Res.*1 (2018): 78-93.
27. He, Y., Wen, Q., Yao, F., Xu, D., Huang, Y. & Wang, J. "Gut-lung axis: The microbial contributions and clinical implications." *Crit. Rev. Microbiol.* 43 (2017): 81-95.
28. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., *et al*. "SARS-coV-2 cell entry depends on ACE2 and TMPRSS 2 and is blocked by a clinically proven protease inhibitor." *Cell.* 181 (2020): 271-280.e8.
29. Holshue, M.L., DeBolt, C., Lindquist, S., Lofy, K.H., Wiesman, J., Bruce, H., *et al*. "First case of 2019 novel coronavirus in the United States." *N. Engl. J. Med.* 382 (2020): 929–936.
30. Hong, G.X. & Pang, S.F. "N-Acetyltransferase activity in the quail (*Coturnixcoturnix japonica*) duodenum." *Comp. Biochem. Physiol.* 112 (1995): 251–255.
31. Hu, L.L., Wang, W.J., Zhu, Q.J. & Yang, L. "Novel coronavirus pneumonia related liver injury: etiological analysis and treatment strategy." *Zhonghua Gan Zang Bing Za Zhi*. 28 (2020): E001.
32. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *Lancet.* 395 (2020): 497-506. DOI: 10.1016/S0140-6736(20)30183-5.
33. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *Lancet (London, England)* 395 (2020): 497–506.
34. Huang, S.H., Cao, X.J., Liu, W., Shi, X.Y. & Wei, W. "Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice." *J. Pineal Res.* 48 (2010): 109–116.
35. Imai, Y., Kuba, K., Neely, G., Yaghubian-Malhami, R., Perkmann, T., *et al*. "Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury." *Cell.* 133 (2008): 235–249.
36. Kaur, C. & Ling, E.A. "Effects of melatonin on macrophages/microglia in postnatal rat brain." *J. Pineal Res.* 26 (1999): 158–168.
37. Kuiken, T., Fouchier, R.A., Schutten, M., Rimmelzwaan, G.F., van Amerongen, G., *et al*. "Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome." *Lancet.* 362 (2003): 263-270.
38. Kvetnoy, I.M., Ingel, I.E., Kvetnaia, T.V., Malinovskaya, N.K., Rapoport, S.I., Raikhlin, N.T., Trofimov, A.V. & Yuzhakov, V.V. "Gastrointestinal melatonin: cellular identification and biological role." *Neuro. Endocrinol. Lett.* 23 (2002): 121–132.
39. Law, H.K.W., Cheung, C.Y., Ng, H.Y., Sia, S.F., Chan, Y.O., Luk, W., Nicholls, J.M., Peiris, J.S.M. & Lau, Y.L. "Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells." *Blood.* 106 (2005): 2366–2374.
40. Leung, J.M., Yang, C.X., Tam, A., Shaipanich, T., Hackett, T.L., Singhera, G.K., Dorscheid, D.R. & Sin, D.D. "ACE-2 expression in the small airway epithelia of smokers and COPD patients: Implications of COVID-19." *European Respiratory Journal* 55.5 (2020).
41. Li, F., Li, W. & Farzan, M. "Structure of SARS coronavirus spike receptor-binding domain complexed with receptor." *Science* 309 (2005): 1864–1868.

Publisher: SARC Publisher

42. Liang, W., Guan, W., Chen, R., Wang, W., Li, J., Xu, K., Li, C., Ai, Q., Lu, W., Liang, H., Li, S. & He, J. "Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China." *Lancet Oncol.* 21 (2020): 335-337.
43. Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., *et al*. "Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury." *Sci. China Life Sci.* (2020).
44. Lopez-Burillo, S., Tan, D.X., Rodriguez-Gallego, V., Manchester, L.C., Mayo, J.C., Sainz, R.M. & Reiter, R.J. "Melatonin and its derivatives cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5- methoxykynuramine, and 6-hydroxymelatonin reduced oxidative damage induced by Fenton reagents." *J. Pineal Res.* 34 (2003): 237–256.
45. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., *et al*. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding." *Lancet.* 395 (2020): 565-574.
46. Mao, R., Liang, J., Shen, J., Ghosh, S., Zhu, L.R., Yang, H., Wu, K.C. & Chen, M.H. "Implications of COVID-19 for patients with pre-existing digestive diseases." *Lancet.* 5 (2020): 426-428.
47. Mauriz, J.L., Collado, P.S., Veneroso, C., Reiter, R.J. & González-Gallego, J. "A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives." *J. Pineal Res.* 54 (2013): 1–14.
48. Mayo, J.C., Aguado, A., Cernuda-Cernuda, R., Álvarez-Artime, A., Cepas, V., Quirós-González, I., Hevia, D. & Sáinz, R.M. "Melatonin uptake by cells: An answer to its relationship with glucose?" *Molecules.* 23 (2018). pii: E1999.
49. Miller, S.C., Pandi-Perumal, S.R., Esquifino, A.I., Cardinali, D.P. & Maestroni, G.J.M. "The role of melatonin in immuno-enhancement: potential application in cancer." *Int. J. Exp. Pathol.* 87 (2006): 81–87.
50. Mistraletti, G., Umbrello, M., Sabbatini, G., Miori, S., Taverna, M., *et al*. "Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial." *Minerva Anestesiol.* 81 (2015): 1298–1310.
51. Mitra, E., Bhattacharjee, B., Pal, P.K., Ghosh, A.K., Mishra, S., Chattopadhyay, A. & Bandyopadhyay, D. "Melatonin protects against cadmium-induced oxidative damage in different tissues of rat: a mechanistic insight." *Melatonin Res.* 2 (2019): 1-21.
52. Ng, S.C. & Tilg, H. "COVID-19 and the gastrointestinal tract: more than meets the eye." *Gut.* (2020) pii: gutjnl-2020-321195. DOI: 10.1136/gutjnl-2020-321195.
53. Nordlund, J.J. & Lerner, A.B. "The effects of oral melatonin on skin color and on the release of pituitary hormones." *J. Clin. Endocrinol. Metab.* 45 (1977): 768–774.
54. Nosál'ová, V., Zeman, M., Černá, S., Navarová, J. & Zakálová, M. "Protective effect of melatonin in acetic acid induced colitis in rats." *J. Pineal Res.* 42 (2007): 364–370.
55. Pal, P.K., Bhattacharjee, B., Ghosh, A., Chattopadhyay, A. & Bandyopadhyay, D. "Adrenaline induced disruption of endogenous melatonergic system, antioxidant and inflammatory responses in the gastrointestinal tissues of male Wistar rat: an *in vitro* study." *Melatonin Res.* 1 (2018): 109–131.
56. Pal, P.K. & Maitra, S.K. "Response of gastrointestinal melatonin, antioxidants, and digestive enzymes to altered feeding conditions in carp (*Catla catla*)." *Fish Physiol. Biochem.* 44 (2018): 1061–1073. https://doi.org/10.1007/s10695-018-0494-0.
57. Pal, P.K., Sarkar, S., Chattopadhyay, A., Tan, D.X. & Bandyopadhyay, D. "Enterochromaffin cells as the source of melatonin: key findings and functional relevance in mammals." *Melatonin Res.* 2 (2019): 61-82.
58. Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., *et al*. "Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study." 115 (2020):766-773.
59. Park, Y.S., Chung, S.H., Lee, S.K., Kim, J.H., Kim, J.B., Kim, T.K., Kim, D.S. & Baik, H.W. "Melatonin improves experimental colitis with sleep deprivation." *Int. J. Mol. Med.* 35 (2015): 979-986.
60. Perlman, S. & Netland, J. "Coronaviruses post-SARS: update on replication and pathogenesis." *Nat. Rev. Microbiol.* 7 (2009): 439-450.
61. Phelan, A.L., Katz, R. & Gostin, L.O. "The novel coronavirus originating in Wuhan, China: Challenges for global health governance." JAMA. (2020).
62. Powers, J.H., Bacci, E.D., Guerrero, M.L., Leidy, N.K., Stringer, S., Kim, K., *et al*. "Reliability, validity, and responsiveness of influenza patient-reported outcome (FLU-PRO©) scores in Influenza-Positive patients." *Value Health.* 21 (2018): 210–218.

Publisher: SARC Publisher

63. Raikhlin, N.T. & Kvetnoy, I.M. "Lightening effect of the extract of human appendix mucosa on frog skin melanophores." *Bull. Exp. Biol. Med.* 8 (1974): 114–116.
64. Reiter, R.J., Calvo, J.R., Karbownik, M., Qi, W. & Tan, D.X. "Melatonin and its relation to the immune system and inflammation." *Ann. N. Y. Acad. Sci.* 917 (2000): 376–386.
65. Reiter, R.J., Ma, Q. & Sharma, R. "Treatment of Ebola and other infectious diseases: melatonin "goes viral"." *Melatonin Res.* 3 (2020): 43–57.
66. Reiter, R.J., Mayo, J.C., Tan, D.X., Sainz, R.M., Alatorre-Jimenez, M. & Qin, L. "Melatonin as an antioxidant: under promises but over delivers." *J. Pineal Res.* 61 (2016): 253–278.
67. Reiter, R.J., Tan, D.X., Acuna-Castroviejo, D., Burkhardt, S. & Karbownik, M. "Melatonin: Mechanisms and actions as an antioxidant." *Curr. Top. Biophys.* 24 (2000): 171–183.
68. Reiter, R.J., Tan, D.X., Manchester, L.C. & Qi, W. "Biochemical reactivity of melatonin with reactive oxygen and reactive nitrogen species: A review of the evidence." *Cell. Biochem. Biophys.* 34 (2001): 237–256.
69. Rodriguez, C., Mayo, J.C., Sainz, R.M., Antolin, I., Herrera, F., Martin, V. & Reiter, R.J. "Regulation of antioxidant enzymes: A significant role for melatonin." *J. Pineal Res.* 36 (2004): 1–9.
70. Saito, S., Tachibana, T., Choi, Y.H., Denbow, D.M. & Furuse, M. "ICV melatonin reduces stress responses in neonatal chicks." *Behav. Brain Res.* 165 (2005): 197–203.
71. Sanchez-Lopez, A.L., Ortiz, G.G., Pacheco-Moises, F.P., Mireles-Ramirez, M.A., Bitzer-Quintero, O.K., Delgado-Lara, D.L.C., Ramirez-Jirano, L.J. & Velazquez- Brizuela, I.E. "Efficacy of melatonin on serum pro-inflammatory cytokines and oxidative stress markers in relapsing remitting multiple sclerosis." *Arch. Med. Res.* 49 (2018): 391–398.
72. Slominski, A., Tobin, D.J., Zmijewski, M.A., Wortsman, J. & Paus, R. "Melatonin in the skin: synthesis, metabolism and functions." *Trends Endocrinol. Metab.*19 (2008): 17–24.
73. Song, W., Gui, M., Wang, X. & Xiang, Y. "Cryo-em structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2." *PLoS Pathog.* 14 (2018): e1007236.
74. Srinivasan, V., Lauterbach, E.C., Ho, K.Y., Acuña-Castroviejo, D., Zakaria, R. & Brzezinski, A. "Melatonin in antinociception: Its therapeutic applications." *Curr. Neuropharmacol.* 10 (2012): 167–178.
75. Su, S., Wong, G., Shi, W., Liu, J., Lai, A.C.K., Zhou, J., Liu, W., Bi, Y. & Gao, G.F. "Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses." *Trends Microbiol*. 24 (2016): 490-502.
76. Sun, C.K., Lee, F.Y., Kao, Y.H., Chiang, H.J., Sung, P.H., Tsai, T.H., Lin, Y.C., Leu, S., Wu, Y.C., Lu, H.I., Chen, Y.L., Chung, S.Y., Su, H.L. & Yip, H.K. "Systemic combined melatonin-mitochondria treatment improves acute respiratory distress syndrome in the rat." J. *Pineal Res.* 58 (2015): 137–150.
77. Tahan, G., Gramignoli, R., Marongiu, F., Aktolga, S., Cetinkaya, A., Tahan, V. & Dorko, K. Melatonin expresses powerful anti-inflammatory and antioxidant activities resulting in complete improvement of acetic-acid-induced colitis in rats. *Dig. Dis. Sci.* 56 (2011): 715-720.
78. Tan, D.X. & Hardeland, R. "Potential utility of melatonin in deadly infectious diseases related to the overreaction of innate immune response and destructive inflammation: focus on COVID-19." *Melatonin Res.* 3 (2020): 120-143.
79. Tan, D.X., Manchester, L.C., Qin, L. & Reiter, R.J. "Melatonin: A mitochondrial targeting molecule involving mitochondrial protection and dynamics." *Int. J. Mol. Sci.* 17 (2016): 2124..
80. Tan, D.X. & Reiter, R. J. "Mitochondria: the birth place, battle ground and the site of melatonin metabolism in cells." *Melatonin Res.* 2 (2019): 44-66.
81. Tan, D.X., Reiter, R.J., Manchester, L.C., Yan, M.T., El-Sawi, M., Sainz, R.M., Mayo, J.C., Kohen, R., Allegra, M. & Hardeland, R. "Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger." *Curr. Top. Med. Chem.* 2 (2002): 181-97.
82. Tang, A., Tong, Z.D., Wang, H.L., Dai, Y.X., Li, K.F., Liu, J.N., Wu, W.J., Yuan, C., Yu, M.L., Li, P. & Yan, J.B. "Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China." *Emerg. Infect. Dis.* 26 (2020).
83. Torres-Farfan, C., Richter, H.G., Rojas-García, P., Vergara, M., Forcelledo, M.L., Valladares, L.E., Torrealba, F., Valenzuela, G.J. & Seron-Ferre, M. "mt1 Melatonin receptor in the

Publisher: SARC Publisher

primate adrenal gland: inhibition of adrenocorticotropin-stimulated cortisol production by melatonin." *J. Clin. Endocrinol. Metab*. 88 (2003): 450–458.
84. Volt, H., García, J.A., Doerrier, C., Díaz-Casado, M.E., Guerra-Librero, A., López, L.C., Escames, G., Tresguerres, J.A. & Acuña-Castroviejo, D. "Same molecule but different expression: aging and sepsis trigger NLRP3 inflammasome activation, a target of melatonin." *J. Pineal Res.* 60 (2016): 193–205.
85. Vriend, J. & Reiter, R.J. "Melatonin as a proteasome inhibitor. Is there any clinical evidence?" *Life Sci.* 115 (2014): 8–14.
86. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., *et al*. "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China." JAMA. (2020).
87. Witt-Enderby, P.A., Radio, N.M., Doctor, J.S. & Davis, V. L. "Therapeutic treatments potentially mediated by melatonin receptors: potential clinical uses in the prevention of osteoporosis, cancer and as an adjuvant therapy." *J. Pineal Res.* 41 (2006): 297–305.
88. Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S. & McLellan, J.S. "Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation." *Science*. 367 (2020): 1260–1263.
89. Wu, X., Ji, H., Wang, Y., Gu, C., Gu, W., Hu, L. & Zhu, L. "Melatonin alleviates radiation-induced lung injury via regulation of miR-30e/NLRP3 axis." *Oxidative medicine and cellular longevity* 2019 (2019): 4087298.
90. Wu, Y., Guo, C., Tang, L., Hong, Z., Zhou, J., Dong, X., Yin, H., Xiao, Q., Tang, Y., Qu, X. and Kuang, L. "Prolonged presence of SARS-CoV-2 viral RNA in faecal samples." *The lancet Gastroenterology & hepatology* 5.5 (2020): 434-435.
91. Xie, C., Jiang, L., Huang, G., Pu, H., Gong, B., Lin, H., Ma, S., Chen, X., Long, B., Si, G. and Yu, H. "Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests." *International Journal of Infectious Diseases* 93 (2020): 264-267.
92. Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W. & Hao, P. "Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission." *Science China Life Sciences* 63.3 (2020): 457-460.
93. Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S. & Shang, Y. "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study." *The Lancet Respiratory Medicine* 8.5 (2020): 475-481.
94. Yao, N., Wang, S.N., Lian, J.Q., Sun, Y.T., Zhang, G.F., Kang, W.Z. & Kang, W. "Clinical characteristics and influencing factors of patients with novel coronavirus pneumonia combined with liver injury in Shaanxi region." *Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology* 28.3 (2020): 234-239.
95. Yip, H.K., Chang, Y.C., Wallace, C.G., Chang, L.T., Tsai, T.H., Chen, Y.L., Chang, H.W., Leu, S., Zhen, Y.Y., Tsai, C.Y., Yeh, K.H., Sun, C.K. & Yen, C.H. "Melatonin treatment improves adipose-derived mesenchymal stem cell therapy for acute lung ischemia–reperfusion injury." *Journal of pineal research* 54.2 (2013): 207-221.
96. Zarezadeh, M., Khorshidi, M., Emami, M., Janmohammadi, P., Kord-Varkaneh, H., Mousavi, S.M., Mohammed, S.H., Saedisomeolia, A. & Alizadeh, S. ""Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials." *European Journal of Nutrition* 59.5 (2020): 1803-1813.
97. Zhang, H., Kang, Z., Gong, H., Xu, D., Wang, J., Li, Z., Li, Z., Cui, X., Xiao, J., Zhan, J., Meng, T., Zhou, W., Liu, J. & Xu, H. "Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process." *Gut.* 0 (2020): 1–9.
98. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L. and Zhang, W., *et al*. "A pneumonia outbreak associated with a new coronavirus of probable bat origin." *Nature.* 579 (2020): 270–273.
99. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R. and Niu, P. "A novel coronavirus from patients with pneumonia in China, 2019." *N. Engl. J. Med.* 382 (2020): 727–733.

Publisher: SARC Publisher

Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:

Pal, P.K. and Panigrahi , A.K. "Implication of Melatonin against COVID-19 Mediated Gastrointestinal Symptoms: An Overview." *Sarcouncil Journal of Internal Medicine and Public Health* 1.1 (2022): pp 1-11

Publisher: SARC Publisher