Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Pharmacology 882 (2020) 173329

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19

Mohamed A. El-Missiry [a,*], Ziad M.A. El-Missiry [b], Azza I. Othman [a]

[a] Zoology Department, Faculty of Science, Mansoura University, Mansoura, Egypt
[b] Department of Oro-maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Mansoura, Egypt

ARTICLE INFO

Keywords:
Covid-19
SARS-CoV-2
Melatonin
Obesity
Diabetes mellitus
Inflammation

ABSTRACT

Coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a newly discovered highly pathogenic virus that was declared pandemic in March 2020 by the World Health Organization. The virus affects the respiratory system, produces an inflammatory storm that causes lung damage and respiratory dysfunction. It infects humans of all ages. The Covid-19 takes a more severe course in individuals with chronic metabolic diseases such as obesity, diabetes mellitus, and hypertension. This category of persons exhibits weak immune activity and decreased levels of endogenous antioxidants. Melatonin is a multifunctional signaling hormone synthesized and secreted primarily by the pineal gland. It is a potent antioxidant with immunomodulatory action and has remarkable anti-inflammatory effects under a variety of circumstances. Regarding Covid-19 and metabolic syndrome, adequate information about the relationship between these two comorbidities is required for better management of these patients. Since Covid-19 infection and complications involve severe inflammation and oxidative stress in people with obesity and diabetes, we anticipated the inclusion of melatonin, as powerful antioxidant, within proposed treatment protocols. In this context, melatonin is a potential and promising agent to help overcome Covid-19 infection and boost the immune system in healthy persons and obese and diabetic patients. This review summarizes some evidence from recently published reports on the utility of melatonin as a potential adjuvant in Covid-19-infected individuals with diabetes and obesity.

1. Introduction

The World Health Organization has declared coronavirus (SARS-CoV-2) as a pandemic on March 11, 2020. The virus is termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and responsible for outbreak of intense respiratory illness named coronavirus disease (Covid-19) (Yuen et al., 2020). This infection first appeared in Wuhan, China, and then spread all over the world and reached all continents and almost all countries (Muniyappa and Gubbi, 2020).

SARS-CoV-2 has a single-stranded RNA and was confirmed to cause respiratory infections and lung injury in humans. The betacoronavirus family includes SARS-CoVs, MERS-CoVs, and SARS-CoV-2. The members of this family share high genetic similarity and induce comparable pathological parameters, particularly oxidative stress and inflammatory effect (Chen, 2020). The respiratory system is the primary target of coronavirus members that induce lung injury and dysfunction leading to fatal pneumonia (Channappanavar and Perlman, 2017). Respiratory dysfunction caused by the continuing outbreak of the novel coronavirus SARS-CoV-2 is a major concern for diabetic and obese individuals worldwide.

Despite the low fatality rate caused by Covid-19 compared with other earlier coronavirus epidemics produced by SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), diabetic and obese people are at a high risk (Yang et al., 2020). Recently, it has been reported that diabetes is an important risk factor for the progression and adverse outcome of Covid-19 and more attention must be paid to diabetic, obese, and hypertensive patients, particularly considering the rapid deterioration (Bloomgarden, 2020; Guo et al., 2020). Therefore, adequate information about the relationship between Covid-19 and metabolic syndrome is required for better management of these patients.

Melatonin (5-methoxy-N-acetyltryptamine) is a neuroendocrine small molecule with a variety of important physiological functions under normal and pathophysiological circumstances.

It is an effective antioxidant and has powerful free radical scavenging activity (Zare Javid et al., 2020). It also stimulates the messenger RNA (mRNA) levels of various antioxidant enzymes. Melatonin possesses

* Corresponding author.
E-mail addresses: maelmissiry@yahoo.com, elmissiry@mans.edu.eg (M.A. El-Missiry).

https://doi.org/10.1016/j.ejphar.2020.173329
Received 25 April 2020; Received in revised form 19 June 2020; Accepted 26 June 2020
Available online 30 June 2020

anti-inflammatory capacity and immunomodulatory activity and effectively boosts the immune system in the body (Reiter et al., 2016). These properties suggest the potential therapeutic use of melatonin to improve clinical outcomes in patients. Accordingly, intervention with antioxidants is a potential approach to overcome oxidative stress and attenuate proinflammatory mediators in diabetic and obese patients. We anticipated that upregulation of the immune system is a potential intervention to block virus progression and consequences. In this context, melatonin is a worthy candidate that can be used to strengthen the immune system against Covid-19 infection and its related complications in obese and diabetic patients.

2. Virus, obesity, diabetes, and inflammation

In metabolic diseases, cell death and oxidative stress are strongly related to inflammation, and changes in proinflammatory cytokines have a strategic position at the crossroad between oxidative stress and inflammation (Muriach et al., 2014). Cytokine dysregulation may be responsible for clinical manifestation, and high levels of proinflammatory biomarkers are a feature in diabetic and obese patients. Moreover, several factors have been suggested to explain the increased susceptibility for SARS-Cov-2 infection in diabetic and obese persons. These factors include weakness of the immune system with increased susceptibility to hyperinflammation and cytokine storm syndrome (Muniyappa and Gubbi, 2020). The term inflammatory or cytokine storm was introduced to underscore the overreaction of the body's immune system and massive production of inflammatory cytokines (Jose and Manuel, 2020). The prevalence of virus infection and its clinical consequences are most featured in older age and in individuals with obesity and diabetes. This category of population exhibits weak immune activity and increased oxidative stress due to the decline in endogenous antioxidants. The levels of inflammatory mediators typically increase with age and metabolic syndrome, even in the absence of acute infection or physiological stress (Cardinali and Hardeland, 2017).These individuals are at a remarkably high risk for hospitalization and death among SARS-CoV-2-infected patients (Muniyappa and Gubbi, 2020).

Obesity is a risk factor for the pathogenesis of diabetes and insulin resistance. It is known that cytokines and inflammatory parameters and other substances involved in insulin resistance are increased in obese individuals (Al-Goblan et al., 2014). In addition, patients with metabolic disorders are more susceptible to oxidative and endoplasmic reticulum stress and inflammation (Alicka and Marycz, 2018). Oxidative stress is caused due to the increased generation of reactive oxygen and nitrogen species over to the ability of the antioxidant system of the body. Oxidative stress is a major depressant of the immune system in the body. It has been reported that patients with T2 diabetes mellitus are vulnerable to infections due to hyperglycemia-induced virulence of various microorganisms (Dworzański et al., 2020).

Earlier studies have shown that infection with Epstein–Barr virus (EBV) is accompanied by increased reactive oxygen species generation and activation of signaling pathways associated with reactive oxygen species (Gargouri et al., 2011; Hu et al., 2017). EBV and SARS-Cov-2 induce an oxidative stress during infection and might contribute to their pathology.

A recent research reported that SARS-Cov-2-infected patients with diabetes were at a higher risk of developing severe pneumonia with uncontrolled inflammatory responses and hypercoagulable state associated with dysregulation of glucose metabolism compared with Covid-19 individuals without DM (Guo et al., 2020). Furthermore, serum levels of inflammatory mediators, including IL-6 and C-reactive protein, were remarkably increased compared to those in nondiabetic patients, suggesting that diabetic patients are more vulnerable to the high inflammatory wave leading to rapid deterioration (Guo et al., 2020). Individuals with diabetes mellitus and severe obesity (BMI $\geq$40 kg/m^2) are more likely to be infected and are at a higher risk for complications and death from Covid-19 (Muniyappa and Gubbi, 2020).

Another recent study reported increased morbidity and mortality in diabetic patients with SARS-CoV-2 infection, indicating that glycemic control is essential in individuals with coexistence of Covid-19 and diabetes (Hill et al., 2020). Similarly, a yet another recent report unveiled the interaction between Covid-19 infection and diabetes as two global pandemics (Maddaloni and Buzzetti, 2020). The authors emphasized that IL-6 is a major inflammatory cytokine whose levels are increased in diabetes and contributed to the susceptibility of diabetic patients to Covid-19 infection and initiation of serious pathological illness. Hence, deactivation of IL-6 receptors is a practical approach for the treatment of Covid-19-induced lung dysfunction in diabetes. A novel study reported that in stressed conditions, it is necessary to improve and optimize the blood glucose management strategy for diabetic patients with Covid-19 infection (Zhou and Tan, 2020). The authors of that study inferred potential and important reasons for the sensitivity of diabetic patients with Covid-19. They demonstrated that a diabetic diet or a personalized diet was unavailable accompanied by the inability of quarantined inpatients to perform exercise due to limited indoor space and poor pulmonary function. In addition, the anxiety caused by Covid-19 induces hyperglycemia (Miazgowski et al., 2018). Finally, the pancreatic tissue is a potential target of viral infection, leading to glucose metabolism disorders (Yang et al., 2010; Zhou and Tan, 2020). Furthermore, a recent report reviewed the possible mechanisms that play significant roles in diabetes mellitus, including the host–viral interactions and the host immune responses (Muniyappa and Gubbi, 2020).

3. Viruses and oxidative stress and inflammation

Coronaviruses can penetrate cells leading to apoptosis and enhance inflammatory responses signified by the activation of pro-inflammatory cytokines that help attract inflammatory cells, including CD+ and T helper (Th-1) cells. SARS-CoV-2 infects immune cells and increases the apoptosis of lymphocytes (CD3, CD4, and CD8 T cells) leading to lymphocytopenia. This results in excessive secretion of pro-inflammatory cytokines in a process termed cytokine storm leading to hyperinflammation and consequent failure of body organs (Deng et al., 2020; Gao et al., 2020).

Infection with the human immunodeficiency virus and hepatitis C virus results in severe inflammation with increased reactive oxygen species production leading to oxidative stress (Gravier-Hernandez et al., 2020). Similarly, oxidative stress-related gene polymorphisms are likely to be associated with hepatitis B virus-induced liver disease, suggesting that information on these variations is useful for risk assessment of HBV-induced liver disease (Ma et al., 2019). An experimental animal study demonstrated an important role of reactive oxygen species in the pathology and immune response to respiratory syncytial virus (RSV). The transcriptional profile of reactive oxygen species -related genes in the respiratory system after RSV infection in the natural host has been discussed recently (Hofstetter and Sacco, 2020). Zika virus (ZIKV) is associated with congenital malformations, and a recent research has reported that astrocytes are the targets of ZIKV. Infection with ZIKV induces mitochondrial dysfunction, oxidative stress, and DNA breakage in human astrocytes (Ledur et al., 2020)

Regarding patients positive with the Epstein–Barr virus, an analysis of antioxidant enzyme activity demonstrated lower activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in patients with diabetes mellitus and obesity than healthy individuals (Dworzański et al., 2020). It has also been reported that chronic infections caused by various viruses influence the entire immunity of diabetic patients. A previous study reported that oxidative stress was induced in infection with the Epstein–Barr virus during the early stages of infection in B lymphocytes and epithelial and lymphoblastoid cell lines. The oxidative stress was manifested by increased lipid peroxidation and decreased activities of CAT and SOD, suggesting an alteration in the molecular mechanisms promoting cellular resistance to reactive oxygen species

(Lassoued et al., 2008). Other studies have demonstrated that oxidative stress and factors leading to DNA damage induce the expression of EBV lytic genes (Arvey et al., 2012; Dworzański et al., 2020; Gargouri et al., 2009).

Mitochondrial reactive oxygen species is a key player in the induction of pathological inflammation during influenza A virus infection in mice. A recent research reported that infection with influenza virus enhanced the production of mitochondrial reactive oxygen species, which induces innate immune inflammation leading to intensification of the viral pathogenesis. This mechanism demonstrated the therapeutic potential of antioxidants to treat influenza virus pathology (To et al., 2020).

Macrophages are essential for innate immune responses and play a remarkable role in protecting animals against viral infections. Infections of macrophages with infectious bronchitis coronavirus (IBV) and Connecticut A5968 (Conn-A5968) strains produced intracellular coronavirus-like particles within cells. IBV causes respiratory defects with increased macrophage count in the respiratory system of animals. When macrophages were infected with IBV and Conn-A5968 strains, the production of the antimicrobial molecule nitric oxide (NO) was inhibited (Amarasinghe et al., 2017). It was also demonstrated that coronaviruses such as SARS-CoV-2 can replicate within human macrophages (Cheung et al., 2005).

Viroporins are virus-encoded proteins that alter membrane permeability and can trigger subsequent cellular signals. Many viruses including corona viruses encode viroporins which are required for maximal viral replication and virulence, as in case of SARS-CoV (Castaño-Rodriguez et al., 2018). Most corona viruses encode two viroporins; E protein and 3a protein, which act as ion-conductive pores in experiments with planar lipid bilayers. SARS-CoV encodes for additional viroporin 8a, which was reported to have less impact on replication and virulence of SARS-CoV than the two other viroporins (Castaño-Rodriguez et al., 2018). They could possibly be responsible for inflammasome activation. Inflammasomes are large multimolecular complexes that can activate caspase-1, which in turn enhances the production of interleukin-1-beta (IL-1β) and interleukin-18 (IL-18). Recent research has reported that viroporin can induce production of IL-1β. Fluxes of potassium, hydrogen, and calcium ions in addition to reactive oxygen species, autophagy, and endoplasmic reticulum stress are involved in this activation (Farag et al., 2020).

4. Melatonin, diabetes, and obesity

Melatonin is a neuroendocrine hormone synthesized and released primarily by the pineal gland. Melatonin is a multifunctional molecule based on its antioxidant activity, direct and indirect free radical scavenging ability to boost the immune system (Mortezaee et al., 2019), and anti-inflammatory actions (Hardeland, 2018).

Melatonin is associated with a variety of signaling mechanisms including the ERK and MAPK pathways (Cui et al., 2008; Sung et al., 2018). In addition, several cell signaling pathways, including ERK1/2-C/EBPα, are involved in the regulatory roles of melatonin in T-cell biology (Ren et al., 2017). Melatonin also stimulated the SIRT1/Nrf2 signaling pathway to reduce lipopolysaccharide-induced reactive oxygen species generation (Shah et al., 2017). Moreover, melatonin ameliorates H_2O_2-induced oxidative stress through modulation of Erk/Akt/NFkB pathway (Moniruzzaman et al., 2018). Melatonin exerts its action directly or indirectly using specific melatonin receptors, MT1 and MT2, on cellular membranes. Melatonin achieves many of its physiological effects by interacting with membrane MT1 and MT2 receptors and intracellular proteins such as quinone reductase 2, calmodulin, calreticulin and tubulin (Pandi-Perumal et al., 2008). Melatonin MT1 and MT2 receptors are G protein coupled receptors which are expressed in various cells in the body organs (Pandi-Perumal et al., 2008). A study using melatonin receptor knock-out mice has indicated an active role of these receptors in the regulation of blood glucose (Muhlbauer et al., 2009). It is also mentioned that melatonin administration normalized metabolic syndrome in elderly hypertensive patients via its receptors (Shatilo et al., 2010).

Blood melatonin levels are continuously decreased with age, exhibiting the highest level at childhood and youth periods and the lowest level in older individuals. Furthermore, at nighttime, the melatonin levels in plasma are higher than those at daytime during the life span. The secretion of melatonin exhibits a circadian rhythm and regulates the sleep/awake cycle (Reutrakul et al., 2018). This explains the deterioration of sleep quality in older people. Moreover, this matches and might explain the higher number of infections, susceptibility to infection, and the severity of Covid-19 symptoms in older persons than in young individuals.

Increased oxidative stress and inflammation are a common feature in patients with diabetes with periodontal diseases. In a double-blind, placebo-controlled trial, supplementation with melatonin was found to significantly increase the serum activities of SOD, CAT, and GPx and decrease lipid peroxidation in diabetic patients with periodontal disease. This effect was accompanied by lower IL-1b levels in melatonin-treated patients than in control individuals (Zare Javid et al., 2020). The treated patients were administered 6 mg melatonin confirming a previous study using 5 mg as an immediate- or sustained-released dose in patients with T2 diabetes (Rybka et al., 2016). Both these studies indicate that melatonin significantly regulated the antioxidant enzymes and increased the total antioxidant capacity in the body. An earlier study reported that “Melatonin is ubiquitous but shows unequal intracellular distribution, including its high concentrations in mitochondria, likely aid in its capacity to resist oxidative stress and cellular apoptosis” (Reiter et al., 2016). Another study reported that melatonin improved the glycemic state and exerted an antioxidant activity by upregulating the GSH content and the activities of SOD, CAT, and glutathione-S-transferase in brain (Gurel-Gokmen et al., 2018). These and several other studies agree on the effectiveness of melatonin to block oxidative stress, inflammation, and cell death and improve organ function in several human trials. The high-safety profile of melatonin also strengthens this conclusion (Reiter et al., 2016).

Diabetes is characterized by hyperglycemia, insulin resistance, dyslipidemia and an augmented inflammatory state (Karamitri and Jockers, 2019). Diabetic patients have lower melatonin levels in blood than healthy people (Reutrakul et al., 2018). Evidence indicating the ability of melatonin to reduce the development of diabetes is derived from the observation that altered glucose metabolism and insulin resistance in shift-workers and high illumination level during night are associated with low blood melatonin levels (Cipolla-Neto et al., 2014). This research group explained that through its receptors, melatonin can regulate GLUT4 expression and initiate the phosphorylation of the insulin receptor and its intracellular substrates mobilizing the insulin-signaling pathway (Cipolla-Neto et al., 2014). The key role of melatonin receptors in the regulation of glucose metabolism was confirmed using melatonin receptor knock-out mice (Muhlbauer et al., 2009).

The reduction in melatonin production, as in elderly people or those with chronic metabolic diseases, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chronodisruption leading to obesity (Cipolla--Neto et al., 2014). These findings indicate that melatonin complementary therapy can play a vital role in reestablishing a more healthy condition of individuals with chronic metabolic diseases.

Increased accumulations of fat in body organs and tissues develop inflammation that can cause several metabolic disorders, including diabetes, hypertension, and dyslipidemia. Due to its antioxidant properties, melatonin treatment can improve the inflammatory mechanisms and energy metabolism. Animal experimental studies have shown that melatonin efficiently decreased the production of blood inflammatory cytokines such as leptin and resistin, reduced adipocyte hypertrophy, and improved the blood lipid profile (Farias et al., 2019). Therefore,

melatonin was termed as a modulator of glucose metabolism. At its pharmacological dose, melatonin enhanced the effects of metformin on insulin sensitivity and body weight gain and when given in combination with metformin, it exhibited a dual therapy for the treatment of diabetes associated with obesity (Dantas-Ferreira et al., 2018). Recently, the latter research group demonstrated that melatonin has a remarkable therapeutic action in decreasing the obesity-induced inflammatory storm. The authors anticipated that melatonin can be used as a low-cost therapeutic agent to improve disorders associated with obesity (de Farias et al., 2019). This confirm previous study that melatonin has antidiabetic and hypolipidemic impact in human and animal model of metabolic syndrome (Cardinali and Hardeland, 2017).

It has been reported that melatonin has immunomodulatory roles with dual proinflammatory and anti-inflammatory actions. The proinflammatory effect is exhibited to fight pathogens, whereas the anti-inflammatory action is manifested in high-grade inflammation in case such as sepsis, oxidative stress, and organ injury and also in low-grade inflammation associated with aging and neurodegenerative diseases (Hardeland, 2018). This double-edge blade of melatonin is attributed to several mechanisms. Besides its ability to downregulate proinflammatory cytokine production and upregulate anti-inflammatory cytokine production, melatonin exhibits high antioxidant capacity and can downregulate inducible nitric oxide synthases and inhibit neuronal nitric oxide synthases, downregulate cyclooxygenase-2, inhibit high-mobility group box-1 signaling and toll-like receptor-4 activation, prevent inflammasome NLRP3 activation, and inhibit NF-κB activation (Hardeland, 2018). In a novel potential therapy using melatonin to prevent and treat obesity caused by systemic inflammatory disease, It is reported that melatonin alleviates adipose tissue inflammation by elevating α-ketoglutarate and diverting adipose-derived exosomes to macrophages in mice (Liu et al., 2018). Based on this information, sustaining normal levels of melatonin in elderly individuals and diabetic and obese people is an important strategy to strengthen the body's defense system and consequently the immune system.

5. Melatonin as an antiviral agent

Melatonin was found to exhibit effective inhibition of pathological manifestations in cases with viral infections in humans (Reiter et al., 2020) and plants (Wang et al., 2020). As SARS-CoV-2 is a newly discovered virus, there is a shortage of research in the literature, which delays the development of effective treatment strategies and in particular the potential effects of melatonin in human or experimental animals against this deadly pathogen. However, melatonin exerts remarkable antiviral effects on several viruses in humans and animals. An early work reported that encephalomyocarditis virus or the Semliki Forest virus causes severe inflammation in the nervous tissue and result in a high mortality rate. Melatonin when administered at the pharmacological dose successfully attenuated the inflammation parameters and reduced the number of deaths (Ben-Nathan et al., 1995; Maestroni et al., 1988). A recent report on Ebola infection demonstrated that the virus hampers the immune system and initiates blood coagulation with significant inflammation reaction that induces an overwhelmed generation of toxic free radicals and the development of oxidative stress and severe damage in cells and tissue. This eventually causes organ and system dysfunction and failure (Reiter et al., 2020). In this regard, these authors reported that melatonin can prevent hemorrhagic shock syndrome, a major pathological parameter, associated with Ebola virus infection. This action is mediated primarily by the reduction of circulating proinflammatory cytokines. Melatonin also upregulates heme oxygenase-1 (HO-1), which obstructs the replication of the Ebola virus (Anderson et al., 2015). Recently, a research group confirmed that melatonin is an effective, safe, and low-cost therapeutic option for Ebola virus (Junaid et al., 2020).

It has also been strongly suggested that melatonin can protect against acute lung injury (ALI)/acute respiratory distress syndrome caused by virus and other pathogens. This is attributed to its well-known anti-inflammatory and antioxidant effects (Zhang et al., 2020b).

Human papillomavirus is associated with oral and genital cancers (D'Souza and Addepalli, 2018; Shafabakhsh et al., 2019). Melatonin exerted a defensive impact on oral cancer and oral ulcer. The preventive and controlling role of melatonin on oral cancer caused due to HPV was attributed primarily to immunoenhancement by increasing T & B lymphocyte activity, increasing monocyte activity, increasing natural killer cell activity, and increasing the secretion of cytokines (IL-6 and IL-2), which ultimately lead to oncostatic activity (D'Souza and Addepalli, 2018). In addition, melatonin in combination with indoleamine 2, 3-dioxygenase-1 inhibitor, administered as an immunometabolic adjuvant, improved the efficacy of immunotherapeutic treatment of HPV-associated tumors (Moreno et al., 2018).

It is possible that melatonin directly interacts with the SARS-CoV-2 membrane and its genetic material. It has been speculated that melatonin can affect the biological activity of viruses. This is supported by the fact that melatonin is a small molecule with amphiphilic nature and can readily cross biological membranes and freely enter all cells and reach subcellular organelles and structures (Amin et al., 2015). In addition, there is evidence indicating that melatonin pleiotropy encompasses the regulation of gene expression through the primary epigenetic mechanisms, including DNA methylation, chromatin modification, and non-coding RNA (Capote-Moreno et al., 2019). Based on these recent findings, comprehensive molecular studies are required to elucidate the ability of melatonin to reverse or inhibit the biological activity of SARS-CoV-2 in diabetic or obese patients. To date, there is no direct experimental evidence on the viricidal effect of melatonin but it has indirect antiviral actions due to its anti-inflammatory, antioxidant, immunomodulatory, and immune enhancing characteristics (Reiter et al., 2020; Zhang et al., 2020b).

In contrast to aforementioned melatonin's immunemodulatory characteristics, other agents showed limited effectiveness in modulating immunoreactivity toward viruses. For instance, statins cannot prevent patients infected with the 2009 H1N1 pandemic influenza from developing severe disease. In addition, there is no direct evidence was shown that angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs), might be effective in the therapy of severe influenza-induced cytokine storm (Liu et al., 2016). Because of the sequence similarity between the spike proteins of SARS-CoV and SARS-CoV-2(Shang et al., 2020), it was recently validated that SARS-CoV-2 also uses ACE2 as its receptor (Zhou et al., 2020). Polyphenols are proved to have immunomodulatory and antioxidant effect in vivo and in vitro however, the major obstacle is their bioavailability and its impact on the biofunctionality. (Yahfoufi et al., 2018).

6. Melatonin is a safe supplement

Melatonin has several properties suggesting its utility in a variety of circumstances. It has high biological safety, and exogenous melatonin can be used in a variety of doses, even including extreme doses (Andersen et al., 2016; Zhang et al., 2020a). It worth mentioning that a melatonin dose of 3–10 mg/day demonstrated acceptable safety level in clinical trials (Chen et al., 2012; Othman et al., 2016; Seabra et al., 2000; Zhang et al., 2020b). Adverse events were generally minor, short-lived, and easily managed (Foley and Steel, 2019). In addition to its high-safety profile, it can be administered through several routes. Melatonin constitutes a natural and easy-to-synthesize product that can be found over shelves with long half-time.

7. Conclusion

This review presents a short brief account of recently published papers on the role of melatonin and its potential benefits, based on which it can be included as a therapeutic adjuvant in the treatment course of Covid-19 patients with chronic diseases. A common trend exists between

the increased number of SARS-COV-2-infected cases and the low levels of blood melatonin in people with chronic metabolic diseases and elderly people. These individuals show decreased levels of endogenous antioxidants, including antioxidant enzymes, and melatonin accompanied by a weak immune system and increased susceptibility to inflammation. The ability of melatonin to decrease viral infections in obese and diabetic patients is attributed to its characteristics such as potent antioxidant effects, improving the endogenous antioxidant system, immunomodulatory, and the strong anti-inflammatory capability. Altogether, these features strongly recommend that melatonin can be useful as a therapeutic option for SARS-COV-2-infected patients with or without chronic metabolic diseases to improve their health. Although there is no direct evidence to support the utility of melatonin in the treatment protocols of Covid-19 patients, extensive data published over the past 50 years recommend its utility.

Funding

None.

Declaration of competing interest

None.

Acknowledgment

We appreciate and thank all the white army, including doctors and nurses, in frontlines in fighting this adverse devastating virus. We shall remember them forever. We also thank Mansoura University that gives great support for fighting this new deadly infection.

References

Al-Goblan, A.S., Al-Alfi, M.A., Khan, M.Z., 2014. Mechanism linking diabetes mellitus and obesity. Diabetes Metab. Syndr. Obes. 7, 587–591. https://doi.org/10.2147/DMSO.S674007, 587-591.

Alicka, M., Marycz, K., 2018. The effect of chronic inflammation and oxidative and endoplasmic reticulum stress in the course of metabolic syndrome and its therapy. Stem Cell. Int. 2018, 4274361. https://doi.org/10.1155/2018/427436.

Amarasinghe, A., Abdul-Cader, M.S., Nazir, S., De Silva Senapathi, U., van der Meer, F., Cork, S.C., Gomis, S., Abdul-Careem, M.F., 2017. Infectious bronchitis corona virus establishes productive infection in avian macrophages interfering with selected antimicrobial functions. PloS One 12 (8), e0181801. https://doi.org/10.1371/journal.pone.0181801.

Amin, A.H., El-Missiry, M.A., Othman, A.I., 2015. Melatonin ameliorates metabolic risk factors, modulates apoptotic proteins, and protects the rat heart against diabetes-induced apoptosis. Eur. J. Pharmacol. 747, 166–173. https://doi.org/10.1016/j.ejphar.2014.12.002.

Andersen, L.P., Gogenur, I., Rosenberg, J., Reiter, R.J., 2016. The safety of melatonin in humans. Clin. Drug Invest. 36 (3), 169–175. https://doi.org/10.1007/s40261-015-0368-5.

Anderson, G., Maes, M., Markus, R.P., Rodriguez, M., 2015. Ebola virus: melatonin as a readily available treatment option. J. Med. Virol. 87 (4), 537–543. https://doi.org/10.1002/jmv.24130.

Arvey, A., Tempera, I., Tsai, K., Chen, H.S., Tikhmyanova, N., Klichinsky, M., Leslie, C., Lieberman, P.M., 2012. An atlas of the Epstein-Barr virus transcriptome and epigenome reveals host-virus regulatory interactions. Cell Host Microbe 12 (2), 233–245. https://doi.org/10.1016/j.chom.2012.06.008.

Ben-Nathan, D., Maestroni, G.J., Lustig, S., Conti, A., 1995. Protective effects of melatonin in mice infected with encephalitis viruses. Arch. Virol. 140, 223–230. https://doi.org/10.1007/BF01309858. Arch Virol.

Bloomgarden, Z.T., 2020. Diabetes and COVID-19. J. Diabetes 12 (4), 347–348. https://doi.org/10.1111/1753-0407.13027.

Capote-Moreno, A., Ramos, E., Egea, J., Lopez-Munoz, F., Gil-Martin, E., Romero, A., 2019. Potential of melatonin as adjuvant therapy of oral cancer in the era of epigenomics. Cancers (Basel) 11 (11), 1712. https://doi.org/10.3390/cancers11111712.

Cardinali, D.P., Hardeland, R., 2017. Inflammaging, metabolic syndrome and melatonin: a call for treatment studies. Neuroendocrinology 104, 382–397. https://doi.org/10.1159/000446543.

Castaño-Rodriguez, C., Honrubia, J.M., Gutiérrez-Álvarez, J., DeDiego, M.L., Nieto-Torres, J.L., Jimenez-Guardeño, J.M., Regla-Nava, J.A., Fernandez-Delgado, R., Verdia-Báguena, C., Queralt-Martín, M., 2018. Role of severe acute respiratory syndrome coronavirus viroporins E, 3a, and 8a in replication and pathogenesis. mBio 9 (3), e02325-17. https://doi.org/10.1128/mBio.02325-17, 2018.

Channappanavar, R., Perlman, S., 2017. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol. 39 (5), 529–539. https://doi.org/10.1007/s00281-017-0629-x.

Chen, J., 2020. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. Microb. Infect. 22 (2), 69–71. https://doi.org/10.1016/j.micinf.2020.01.004.

Chen, Y.C., Tain, Y.L., Sheen, J.M., Huang, L.T., 2012. Melatonin utility in neonates and children. J. Formos. Med. Assoc. 111 (2), 57–66. https://doi.org/10.1016/j.jfma.2011.11.024.

Cheung, C.Y., Poon, L.L., Ng, I.H., Luk, W., Sia, S.F., Wu, M.H., Chan, K.H., Yuen, K.Y., Gordon, S., Guan, Y., Peiris, J.S., 2005. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J. Virol. 79 (12), 7819–7826. https://doi.org/10.1128/JVI.79.12.7819-7826.2005.

Cipolla-Neto, J., Amaral, F.G., Afeche, S.C., Tan, D.X., Reiter, R.J., 2014. Melatonin, energy metabolism, and obesity: a review. J. Pineal Res. 56 (4), 371–381. https://doi.org/10.1111/jpi.12137.

Cui, P., Yu, M., Luo, Z., Dai, M., Han, J., Xiu, R., Yang, Z., 2008. Intracellular signaling pathways involved in cell growth inhibition of human umbilical vein endothelial cells by melatonin. J. Pineal Res. 44 (1), 107–114. https://doi.org/10.1111/j.1600-079X.2007.00496.x.

D'Souza, S., Addepalli, V., 2018. Preventive measures in oral cancer: an overview. Biomed. Pharmacother. 107, 72–80. https://doi.org/10.1016/j.biopha.2018.07.114.

Dantas-Ferreira, R.F., Raingard, H., Dumont, S., Schuster-Klein, C., Guardiola-Lemaitre, B., Pevet, P., Challet, E., 2018. Melatonin potentiates the effects of metformin on glucose metabolism and food intake in high-fat-fed rats. Endocrinol Diabetes Metab 1 (4), e00039. https://doi.org/10.1002/edm2.39.

de Farias, T., Cruz, M.M., de Sa, R., Severi, I., Perugini, J., Senzacqua, M., Cerutti, S.M., Giordano, A., Cinti, S., Alonso-Vale, M.I.C., 2019. Melatonin supplementation decreases hypertrophic obesity and inflammation induced by high-fat diet in mice. Front. Endocrinol. 10, 750. https://doi.org/10.3389/fendo.2019.00750.

Deng, Y., Liu, W., Liu, K., Fang, Y.Y., Shang, J., Zhou, L., Wang, K., Leng, F., Wei, S., Chen, L., Liu, H.G., 2020. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). https://doi.org/10.1097/CM9.0000000000000824.

Dworzański, J., Strycharz-Dudziak, M., Kliszczewska, E., Kiełczykowska, M., Dworzańska, A., Drop, B., Polz-Dacewicz, M., 2020. Glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity in patients with diabetes mellitus type 2 infected with Epstein-Barr virus. PloS One 15 (3), e0230374. https://doi.org/10.1371/journal.pone.0230374.

Farag, N.S., Breitinger, U., Breitinger, H.G., El Azizi, M.A., 2020. Viroporins and inflammasomes: a key to understand virus-induced inflammation. Int. J. Biochem. Cell Biol. 122, 105738. https://doi.org/10.1016/j.biocel.2020.105738.

Farias, T., Paixao, R.I.D., Cruz, M.M., de Sa, R., Simao, J.J., Antraco, V.J., Alonso-Vale, M.I.C., 2019. Melatonin supplementation attenuates the pro-inflammatory adipokines expression in visceral fat from obese mice induced by A high-fat diet. Cells 8 (9), 1041. https://doi.org/10.3390/cells8091041.

Foley, H.M., Steel, A.E., 2019. Adverse events associated with oral administration of melatonin: a critical systematic review of clinical evidence. Compl. Ther. Med. 2019 (42), 65–81. https://doi.org/10.1016/j.ctim.2018.11.003.

Gao, Y., Li, T., Han, M., Li, X., Wu, D., Xu, Y., Zhu, Y., Liu, Y., Wang, X., Wang, L., 2020. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J. Med. Virol. https://doi.org/10.1002/jmv.25770, 10.1002/jmv.25770.

Gargouri, B., Nasr, R., ben Mansour, R., Lassoued, S., Mseddi, M., Attia, H., El Feki, A.e. F., Van Pelt, J., 2011. Reactive oxygen species production and antioxidant enzyme expression after Epstein–Barr virus lytic cycle induction in Raji cell line. Biol. Trace Elem. Res. 144 (1-3), 1449–1457. https://doi.org/10.1007/s12011-011-9135-5.

Gargouri, B., Van Pelt, J., El Feki Ael, F., Attia, H., Lassoued, S., 2009. Induction of Epstein-Barr virus (EBV) lytic cycle in vitro causes oxidative stress in lymphoblastoid B cell lines. Mol. Cell. Biochem. 324 (1-2), 55–63. https://doi.org/10.1007/s11010-008-9984-1.

Gravier-Hernandez, R., Gil-Del Valle, L., Valdes-Alonso, L., Hernandez-Ayala, N., Bermudez-Alfonso, Y., Hernandez-Requejo, D., Rosell-Guerra, T., Hernandez-Gonzalez-Abreu, M.C., 2020. Oxidative stress in hepatitis C virus-human immunodeficiency virus co-infected patients. Ann. Hepatol. 19 (1), 92–98. https://doi.org/10.1016/j.aohep.2019.05.009.

Guo, W., Li, M., Dong, Y., Zhou, H., Zhang, Z., Tian, C., Qin, R., Wang, H., Shen, Y., Du, K., Zhao, L., Fan, H., Luo, S., Hu, D., 2020. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev, e3319. https://doi.org/10.1002/dmrr.3319.

Gurel-Gokmen, B., Ipekci, H., Oktay, S., Alev, B., Ustundag, U.V., Ak, E., Akakin, D., Sener, G., Emekli-Alturfan, E., Yarat, A., Tunali-Akbay, T., 2018. Melatonin improves hyperglycemia induced damages in rat brain. Diabetes Metab Res Rev 34 (8), e3060. https://doi.org/10.1002/dmrr.3060.

Hardeland, R., 2018. Melatonin and inflammation-Story of a double-edged blade. J. Pineal Res. 65 (4), e12525 https://doi.org/10.1111/jpi.12525.

Hill, M.A., Mantzoros, C., Sowers, J.R., 2020. Commentary: COVID-19 in patients with diabetes. Metabolism 107, 154217. https://doi.org/10.1016/j.metabol.2020.154217.

Hofstetter, A.R., Sacco, R.E., 2020. Oxidative stress pathway gene transcription after bovine respiratory syncytial virus infection in vitro and ex vivo. Vet. Immunol. Immunopathol. 219, 109956. https://doi.org/10.1016/j.vetimm.2019.109956.

Hu, J., Li, H., Luo, X., Li, Y., Bode, A., Cao, Y., 2017. The role of oxidative stress in EBV lytic reactivation, radioresistance and the potential preventive and therapeutic implications. Int. J. Canc. 141 (9), 1722–1729. https://doi.org/10.1002/ijc.30816.

Jose, R.J., Manuel, A., 2020. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med S2213–2600 (20). https://doi.org/10.1016/S2213-2600(20)30216-2, 30216-2.

Junaid, A., Tang, H., van Reeuwijk, A., Abouleila, Y., Wuelfroth, P., van Duinen, V., Stam, W., van Zonneveld, A.J., Hankemeier, T., Mashaghi, A., 2020. Ebola hemorrhagic shock syndrome-on-a-chip. iScience 23 (1), 100765. https://doi.org/10.1016/j.isci.2019.100765.

Karamitri, A., Jockers, R., 2019. Melatonin in type 2 diabetes mellitus and obesity. Nat. Rev. Endocrinol. 15 (2), 105–125. https://doi.org/10.1038/s41574-018-0130-1.

Lassoued, S., Ben Ameur, R., Ayadi, W., Gargouri, B., Ben Mansour, R., Attia, H., 2008. Epstein-Barr virus induces an oxidative stress during the early stages of infection in B lymphocytes, epithelial, and lymphoblastoid cell lines. Mol. Cell. Biochem. 313 (1-2), 179–186. https://doi.org/10.1007/s11010-008-9755-z.

Ledur, P.F., Karmirian, K., Pedrosa, C., Souza, L.R.Q., Assis-de-Lemos, G., Martins, T.M., Ferreira, J., de Azevedo Reis, G.F., Silva, E.S., Silva, D., Salerno, J.A., Ornelas, I.M., Devalle, S., Madeiro da Costa, R.F., Goto-Silva, L., Higa, L.M., Melo, A., Tanuri, A., Chimelli, L., Murata, M.M., Garcez, P.P., Filippi-Chiela, E.C., Galina, A., Borges, H.L., Rehen, S.K., 2020. Zika virus infection leads to mitochondrial failure, oxidative stress and DNA damage in human iPSC-derived astrocytes. Sci. Rep. 10 (1), 1218. https://doi.org/10.1038/s41598-020-57914-x.

Liu, Q., Zhou, Y.H., Yang, Z.Q., 2016. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell. Mol. Immunol. 13 (1), 3–10. https://doi.org/10.1038/cmi.2015.74.

Liu, Z., Gan, L., Zhang, T., Ren, Q., Sun, C., 2018. Melatonin alleviates adipose inflammation through elevating alpha-ketoglutarate and diverting adipose-derived exosomes to macrophages in mice. J. Pineal Res. 64 (1) https://doi.org/10.1111/jpi.12455, 10.1111/jpi.12455.

Ma, N., Liu, W., Zhang, X., Gao, X., Yu, F., Guo, W., Meng, Y., Gao, P., Zhou, J., Yuan, M., Mi, Y., Zhang, L., Qi, S., Li, L., Wang, L., Su, Q., Yang, L., Liu, D., 2019. Oxidative stress-related gene polymorphisms are associated with hepatitis B virus-induced liver disease in the northern Chinese han population. Front. Genet. 10, 1290. https://doi.org/10.3389/fgene.2019.01290.

Maddaloni, E., Buzzetti, R., 2020. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev, e33213321. https://doi.org/10.1002/dmrr.3321.

Maestroni, G.J., Conti, A., Pierpaoli, W., 1988. Pineal melatonin, its fundamental immunoregulatory role in aging and cancer. Ann. N. Y. Acad. Sci. 521, 140–148. https://doi.org/10.1111/j.1749-6632.1988.tb35272.x.

Miazgowski, T., Bikowska, M., Ogonowski, J., Taszarek, A., 2018. The impact of Health locus of control and anxiety on self-monitored blood glucose concentration in women with gestational diabetes mellitus. J Womens Health (Larchmt). 27 (2), 209–215. https://doi.org/10.1089/jwh.2017.6366.

Moniruzzaman, M., Ghosal, I., Das, D., Chakraborty, S.B., 2018. Melatonin ameliorates H2O2-induced oxidative stress through modulation of Erk/Akt/NFkB pathway. Biol. Res. 51 (1), 17. https://doi.org/10.1186/s40659-018-0168-5.

Moreno, A.C.R., Porchia, B., Pagni, R.L., Souza, P.D.C., Pegoraro, R., Rodrigues, K.B., Barros, T.B., Aps, L., de Araujo, E.F., Calich, V.L.G., Ferreira, L.C.S., 2018. The combined use of melatonin and an indoleamine 2,3-dioxygenase-1 inhibitor enhances vaccine-induced protective cellular immunity to HPV16-associated tumors. Front. Immunol. 9, 1914. https://doi.org/10.3389/fimmu.2018.01914.

Mortezaee, K., Potes, Y., Mirtavoos-Mahyari, H., Motevaseli, E., Shabeeb, D., Musa, A.E., Najafi, M., Farhood, B., 2019. Boosting immune system against cancer by melatonin: a mechanistic viewpoint. Life Sci. 238, 116960. https://doi.org/10.1016/j.lfs.2019.116960.

Muhlbauer, E., Gross, E., Labucay, K., Wolgast, S., Peschke, E., 2009. Loss of melatonin signalling and its impact on circadian rhythms in mouse organs regulating blood glucose. Eur. J. Pharmacol. 606 (1-3), 61–71. https://doi.org/10.1016/j.ejphar.2009.01.029.

Muniyappa, R., Gubbi, S., 2020. COVID-19 pandemic, corona viruses, and diabetes mellitus. Am. J. Physiol. Endocrinol. Metab. 318, E736–E741. https://doi.org/10.1152/ajpendo.00124.2020.

Muriach, M., Flores-Bellver, M., Romero, F.J., Barcia, J.M., 2014. Diabetes and the brain: oxidative stress, inflammation, and autophagy. Oxid Med Cell Longev 2014, 102158. https://doi.org/10.1155/2014/102158.

Othman, A.I., Edrees, G.M., El-Missiry, M.A., Ali, D.A., Aboel-Nour, M., Dabdoub, B.R., 2016. Melatonin controlled apoptosis and protected the testes and sperm quality against bisphenol A-induced oxidative toxicity. Toxicol. Ind. Health 32 (9), 1537–1549. https://doi.org/10.1177/0748233714561286.

Pandi-Perumal, S.R., Trakht, I., Srinivasan, V., Spence, D.W., Maestroni, G.J., Zisapel, N., Cardinali, D.P., 2008. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol 85 (3), 335–353. https://doi.org/10.1016/j.pneurobio.2008.04.001.

Reiter, R.J., Ma, Q., Sharma, R., 2020. Treatment of Ebola and other infectious diseases: melatonin "goes viral". Melatonin Res 3 (1), 43–57. https://doi.org/10.32794/mr11250047.

Reiter, R.J., Mayo, J.C., Tan, D.X., Sainz, R.M., Alatorre-Jimenez, M., Qin, L., 2016. Melatonin as an antioxidant: under promises but over delivers. J. Pineal Res. 61, 253–278.

Ren, W., Liu, G., Chen, S., Yin, J., Wang, J., Tan, B., Wu, G., Bazer, F.W., Peng, Y., Li, T., Reiter, R.J., Yin, Y., 2017. Melatonin signaling in T cells: functions and applications. J. Pineal Res. 62 (3) https://doi.org/10.1111/jpi.12394, 10.1111/jpi.12394.

Reutrakul, S., Sumritsopak, R., Saetung, S., Chanprasertyothin, S., Chailurkit, L.O., Anothaisintawee, T., 2018. Lower nocturnal urinary 6-sulfatoxymelatonin is associated with more severe insulin resistance in patients with prediabetes. Neurobiol Sleep Circadian Rhythms 4, 10–16. https://doi.org/10.1016/j.nbscr.2017.06.001.

Rybka, J., Kedziora-Kornatowska, K., Kupczyk, D., Muszalik, M., Kornatowski, M., Kedziora, J., 2016. Antioxidant effect of immediate- versus sustained-release melatonin in type 2 diabetes mellitus and healthy controls. Drug Deliv. 23 (3), 814–817. https://doi.org/10.3109/10717544.2014.917343.

Seabra, M.L., Bignotto, M., Pinto Jr., L.R., Tufik, S., 2000. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. J. Pineal Res. 29 (4), 193–200. https://doi.org/10.1034/j.1600-0633.2002.290401.x.

Shafabakhsh, R., Reiter, R.J., Mirzaei, H., Teymoordash, S.N., Asemi, Z., 2019. Melatonin: a new inhibitor agent for cervical cancer treatment. J. Cell. Physiol. 234 (12), 21670–21682. https://doi.org/10.1002/jcp.28865.

Shah, S.A., Khan, M., Jo, M.H., Jo, M.G., Amin, F.U., Kim, M.O., 2017. Melatonin stimulates the SIRT1/nrf2 signaling pathway counteracting lipopolysaccharide (LPS)-Induced oxidative stress to rescue postnatal rat brain. CNS Neurosci. Ther. 23 (1), 33–44. https://doi.org/10.1111/cns.12588.

Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., Geng, Q., Auerbach, A., Li, F., 2020. Structural basis of receptor recognition by SARS-CoV-2. Nature 581 (7807), 221–224. https://doi.org/10.1038/s41586-020-2179-y, 2020.

Shatilo, V.B., Bondarenko, E.V., Antoniuk-Shcheglova, I.A., 2010. Pineal gland melatonin-producing function in elderly patients with hypertensive disease: age peculiarities. Adv. Gerontol. 23 (4), 539–542. Advances in gerontology = Uspekhi gerontologii 23, 539-542.

Sung, J.Y., Bae, J.H., Lee, J.H., Kim, Y.N., Kim, D.K., 2018. The melatonin signaling pathway in a long-term memory in vitro study. Molecules 23 (4), 737. https://doi.org/10.3390/molecules23040737.

To, E.E., Erlich, J.R., Liong, F., Luong, R., Liong, S., Esaq, F., Oseghale, O., Anthony, D., McQualter, J., Bozinovski, S., Vlahos, R., O'Leary, J.J., Brooks, D.A., Selemidis, S., 2020. Mitochondrial reactive oxygen species contribute to pathological inflammation during influenza A virus infection in mice. Antioxidants Redox Signal. 32 (13), 929–942. https://doi.org/10.1089/ars.2019.7727.

Wang, M., Zhang, S., Ding, F., 2020. Melatonin mitigates chilling-induced oxidative stress and photosynthesis inhibition in tomato plants. Antioxidants (Basel) 9 (3), 218. https://doi.org/10.3390/antiox9030218.

Yahfoufi, N., Alsadi, N., Jambi, M., Matar, C., 2018. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients 10 (11), 1618. https://doi.org/10.3390/nu10111618.

Yang, J.K., Lin, S.S., Ji, X.J., Guo, L.M., 2010. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 47 (3), 193–199. https://doi.org/10.1007/s00592-009-0109-4.

Yang, S., Cao, P., Du, P., Wu, Z., Zhuang, Z., Yang, L., Yu, X., Zhou, Q., Feng, X., Wang, X., Li, W., Liu, E., Chen, J., Chen, Y., He, D., 2020. Early estimation of the case fatality rate of COVID-19 in mainland China: a data-driven analysis. Ann. Transl. Med. 8 (4), 128. https://doi.org/10.21037/atm.2020.02.66.

Yuen, K.S., Ye, Z.W., Fung, S.Y., Chan, C.P., Jin, D.Y., 2020. SARS-CoV-2 and COVID-19: the most important research questions. Cell Biosci. 10, 40. https://doi.org/10.1186/s13578-020-00404-4.

Zare Javid, A., Hosseini, S.A., Gholinezhad, H., Moradi, L., Haghighi-Zadeh, M.H., Bazyar, H., 2020. Antioxidant and anti-inflammatory properties of melatonin in patients with type 2 diabetes mellitus with periodontal disease under non-surgical periodontal therapy: a double-blind, placebo-controlled trial. Diabetes Metab Syndr Obes 13, 753-761. https://doi.org/10.2147/DMSO.S242208.

Zhang, J., Yan, X., Tian, Y., Li, W., Wang, H., Li, Q., Li, Y., Li, Z., Wu, T., 2020a. Synthesis of a new water-soluble melatonin derivative with low toxicity and a strong effect on sleep aid. ACS Omega 5 (12), 6494-6499. https://doi.org/10.1021/acsomega.9b04120.

Zhang, R., Wang, X., Ni, L., Di, X., Ma, B., Niu, S., Liu, C., Reiter, R.J., 2020b. COVID-19: melatonin as a potential adjuvant treatment. Life Sci. 250, 117583. https://doi.org/10.1016/j.lfs.2020.117583.

Zhou, J., Tan, J., 2020. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism 107, 154216. https://doi.org/10.1016/j.metabol.2020.154216.

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579 (7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7, 2020.