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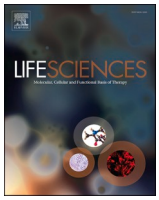

Review article

# Melatonin effect on platelets and coagulation: Implications for a prophylactic indication in COVID-19

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ABSTRACT

Severe COVID-19 is associated with the dynamic changes in coagulation parameters. Coagulopathy is considered as a major extra-pulmonary risk factor for severity and mortality of COVID-19; patients with elevated levels of coagulation biomarkers have poorer in-hospital outcomes. Oxidative stress, alterations in the activity of cytochrome P450 enzymes, development of the cytokine storm and inflammation, endothelial dysfunction, angiotensin-converting enzyme 2 (ACE2) enzyme malfunction and renin–angiotensin system (RAS) imbalance are among other mechanisms suggested to be involved in the coagulopathy induced by severe acute respiratory syndrome coronavirus (SARS-CoV-2). The activity and function of coagulation factors are reported to have a circadian component. Melatonin, a multipotential neurohormone secreted by the pineal gland exclusively at night, regulates the cytokine system and the coagulation cascade in infections such as those caused by coronaviruses. Herein, we review the mechanisms and beneficial effects of melatonin against coagulopathy induced by SARS-CoV-2 infection.

## 1. Introduction

In December 2019, the outbreak of pneumonia of unknown region was reported in China. Soon thereafter, the disease spread globally and claimed more than 5.3 million lives by December 2021. Further investigations revealed the severe acute respiratory syndrome coronavirus (SARS-CoV-2) as the responsible pathogen, a novel beta coronavirus and the successor of SARS-CoV and Middle east respiratory syndrome coronavirus (MERS-CoV) which had 10 % and 35 % mortality rates, respectively [1]. Analyses have revealed significant clinical and structural overlap between SARS-CoV-2 and SARS-CoV since they exhibit 80 % sequence similarity [2]. SARS-CoV-2 is a zoonotic virus which exhibits human-to- human transmission through airborne particles and droplets which mainly enter via the respiratory route. Other avenues of infection including orofecal, conjunctival and vertical transmission through pregnancy have also been frequently documented. In addition, the virus has relatively long incubation and shedding periods, which significantly aids its spread and evasion during routine analysis [3]. Although a considerable percentage of those infected with the virus remain asymptomatic, disease manifestation in the early stages includes fever, sore throat, dry cough, headache, fatigue, restlessness, myalgia, anosmia, and dysgeusia, which may later evolve into more serious conditions such as acute respiratory distress syndrome (ARDS).

SARS-CoV-2 infections are associated with dynamic changes in coagulation parameters when they become severe. Coagulopathy is considered as a major extrapulmonary risk factor for disease severity and mortality of COVID-19 patients and early detection of elevated coagulation biomarkers are useful for predicting higher risk stratification and poorer outcomes of infected patients [4]. Herein, we describe coagulation parameters alterations during a SARS-CoV-2 infection, and follow this with a description of the potential modulatory effects of melatonin on coagulation pathways.

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## 2. Covid-19: pathogenesis, clinical manifestations and complications

SARS-CoV-2 gains cell entry through transmembrane protease serine 2 (TMPRSS2) and lysosomal proteases via two independent mechanisms including cleavage of coronavirus spike glycoproteins (cell entry glycoprotein activation) and the proteolytic cleavage of angiotensin-converting enzyme-2 (ACE-2) receptor both of which increase viral uptake by host cells [5]. Cell entry is initiated upon the attachment of the virus spike proteins to the ACE-2 protein [6,7]. In humans, ACE-2 is expressed by an array of cells including the pneumocytes of the alveolar sacs, vascular endothelium, cardiovascular tissue, renal tissue, and intestinal epithelia [6,7]. This diverse distribution may explain the multiorgan involvement of this infection as well as contributing to disease severity in individuals infected with SARS-CoV-2. The ACE-2 expression in endothelial cells is controversial. In a study conducted by McCracken, the expression of ACE2 in endothelial cells has been not found and it is suggested that SARS-CoV-2 could not directly infects endothelial cells [8]. However, Costa et 2021 demonstrated the expression of ACE 2 and TMPRSS2 proteins in HUVECs infected by SARS-CoV-2 [9]. In Covid-19 infected patients, interstitial pneumonia is the hallmark involvement of the pulmonary system and if left untreated it may result in hypoxia, ARDS, systemic inflammatory response syndrome (SIRS) and multiorgan failure (MOF) [10]. The expression of ACE-2 receptors on cells in addition to those on the respiratory alveolar lining cells may account for the widespread extrapulmonary damage in the setting of COVID-19. The involvement of other organs presents organ-specific symptoms. For example, the involvement of the gastrointestinal tract causes nausea, vomiting, diarrhoea and abdominal pain. In addition, hepatic injury, as reflected in circulating elevated liver enzymes, are also common. Peripheral and central nervous system involvement is associated with headache, dizziness, encephalopathy, hyposmia (or anosmia), neuralgia, and Guillian-Barre syndrome [11]. In the cardiovascular system, infection with SARS-CoV-2 may result in the development of acute coronary syndrome, cardiomyopathies, arrythmias, pericarditis, and thromboembolic events [12–14]. The latter is more commonly observed in hospitalized patients and has been identified as an independent prognostic risk factor.

SARS-CoV-2 infections also result in the development of coagulopathies, the most common of which is thrombocytopenia; this is most frequently observed in critically ill patients. A meta-analysis of 3342 patients with COVID-19 showed that the incidence rates of pulmonary embolism (PE) and deep vein thrombosis (DVT) were around 16.5 % (95 % CI: 11.6–22.9) and 14.8 % (95 % CI: 8.5–24.5), respectively; PE was more frequently identified in intensive care unit (ICU) patients (24.7 %) compared to those with a less serious condition. COVID-19 associated acute kidney injury (AKI) is also observed in an estimated 25 % of hospitalized patients, rendering it yet another independent risk factor for in-hospital mortality. The pathophysiology of AKI in COVID-19 is multi-factorial, arising from inflammatory and immune responses, activation of coagulation pathways and the renin–angiotensin system [15]. Importantly, it should be noted that COVID-19-associated coagulopathies appear to be crucial in the development of extrapulmonary complications. Collectively, the published literature confirms that COVID-19 is not a mere viral pneumonia and the development of MOF is to be expected in severe cases. Therefore, a systemic treatment approach is crucial to completely counter the effects of this viral infection.

## 3. Melatonin, a multipotential agent in different diseases

Melatonin, *N*-acetyl-5-methoxytryptamine, is a secretory product of the pineal gland and is mainly released at night. Additionally, melatonin is also synthesized in the retina, kidneys, gastrointestinal tract, skin and other organs [16–18]. This molecule is found both in animals and plants [19] and in the plants melatonin may be produced in both mitochondria and chloroplasts [20].

Melatonin is primarily considered a hormone that influences numerous biological events such as modulating the release of other hormones, apoptosis and immune responses among others. Furthermore, melatonin has oncostatic, anti-inflammatory and antioxidant properties (21)features highlight the potential role of melatonin as a treatment of many diseases. Melatonin is considered a natural sleep-aid compound and regulates different physiological events including the sleep-wake cycle and other circadian rhythms [22]. The prophylactic and therapeutic effects of melatonin have been extensively addressed in a number of neurological disorders including Parkinson's disease [23,24], amyotrophic lateral sclerosis, multiple sclerosis [25], Alzheimer's disease [26,27], headache, epilepsy, and Huntington's disease [28]. Moreover, anti-depressive actions of melatonin are noted in LPS-induced depression; this action is thought to be mediated via the modulation of autophagy [29]. Of note, melatonin has been shown to exert anti-aging effects and could be used for the management and treatment of age-related diseases in humans [30].

The ability of melatonin to prevent oxidative damage and its pathophysiological consequences is well documented in numerous experimental ischemia/reperfusion studies, particularly in myocardial infarction and stroke [25]. Clinical data obtained from human beings indicate that the use of melatonin helps to lower blood pressure in patients with hypertension. Several lines of evidence have demonstrated that administration of melatonin to experimental animals leads to the improvement of cardiac function and the reduction of cardiomyocyte injury induced by ischemia/reperfusion. Also, melatonin markedly attenuates the adverse effects caused by the use of cardiotoxic drugs by cancer patients [31]. Moreover, the beneficial impact of melatonin on coagulopathy has been reported by several studies.

In addition to its ability to prevent the loss of normal cells due to its anti-apoptotic properties, melatonin exerts anti-proliferative and pro-apoptotic activities on cancer cells; indeed, melatonin has been widely tested for its oncostatic actions [32]. Based on both in vitro and in vivo data and preclinical studies, melatonin defers the development of tumors via both membrane-independent and –dependent mechanisms. Its inhibitory effect on cancer is manifested at the initiation, development, progression, and the metastatic phase of tumorigenesis [33]. As a result of its anti-metastatic, anti-angiogenic, and anti-proliferative activity, melatonin could be employed for the treatment for many types of malignancies, especially for those that have a high tendency to metastasize. Furthermore, melatonin has synergistic effects with conventional therapies used for the treatment of malignancies; the combination of melatonin with chemotherapeutic agents increases the sensitivity of cancer cells to undergo apoptosis [21]. Since melatonin scavenges free radicals, it also has been used to neutralize the toxic side effects of some chemical compounds such as methamphetamine [25]. A number of studies have documented the ability of melatonin in neutralizing the effects of nematocyst and snake venom toxins which are largely a result of massive free radical generation [34,35]. The use of melatonin as an anti-viral agent has recently come into focus as well and it has been proposed as a treatment for Ebola, COVID-19 and other viral infections [36,37]. There are currently 185 publications suggesting the utility of melatonin to treat COVID and all it variants [38–40]. The first of these reports appeared within two months after the COVID infection was recognized as a pandemic [41].

The results of many studies indicated that the anti-inflammatory actions of melatonin involve the suppression of IFN-alpha, MCP-1, tumor necrosis factor alpha (TNF-α), IL-6, IL-8, as well as the inhibition of JNK phosphorylation and promotion of the degradation of proteins which are responsible for the integrity of tight junction [42]. Furthermore, melatonin reduces the apoptosis rate of endothelial cells [43–45]. The maintenance of vascular integrity and protecting endothelial cells against injury are among the mechanistic roles of melatonin in the fatal hemorrhage at the late phase of Ebola virus infection [46]. In brief, melatonin exerts a broad range of biological activities including neuroprotection, immunomodulation, regulation of reproduction,

prevention of tumorigenesis, protection of gastrointestinal function, and it exhibits anti-aging actions [47].

## 4. Melatonin and coagulation cascade parameters

Hemostasis is an intricate balance of numerous molecules, cells, and pathways influenced by many intrinsic and extrinsic factors. Like many other processes, the machinery of coagulation and fibrinolysis differs throughout the circadian cycle. Platelet count and function, the activity of the procoagulant, anticoagulant, and fibrinolytic factors, as well as the endothelial function, are influenced by the circadian system [48]. In general, diurnal changes have been observed in the form of increased platelet activity and aggregation, enhanced vasoconstriction, elevated activity of the factors VII and VIII and the von Willebrand factor, as well as higher protein —C and —S and tissue plasminogen activator are reported in the early light period [49,50]. In contrast, a marked increased activity occurs in the early evening and night hours, as evidenced by reduced endothelial reactivity, increased secretion of tissue plasminogen activator inhibitor, and decreased platelet hyperreactivity compared to early daytime [51].

The role of melatonin in regulating hemostasis and fibrinolysis, although previously investigated, remains to be fully elucidated. The administration of melatonin has been proposed to treat many emerging diseases, the most recent being the Ebola virus, due to its role as a regulator of the cytokine system and coagulation cascade [52]. The effect of melatonin on platelet function varies in accordance with serum levels. At physiologic concentrations, platelet aggregation is promoted, while in therapeutic doses, thrombosis is an expected event [53].

Pashalieva and colleagues observed that the administration of melatonin (3 days, twice daily, 0.2 mg/kg) in a rat model was associated with a significant elevation in thrombocyte count and plasma markers of platelet activity β-TG and PF-4, while the administration of luzindole, a melatonin receptor blocker, prevented these changes [54,55]. Another study demonstrated that the administration of the same doses of melatonin caused a reduction of activated partial thromboplastin time (aPTT), prothrombin time and thrombin time [56]. Lansik and colleagues reported that administration of melatonin (3 mg/kg) 15 min prior and 120 and 240 min after the induction of disseminated intravascular coagulation (DIC) due to lipopolysaccharide administration (0.5/kg/h for 3 h) was solely successful in ameliorating reduced platelet counts and cell-free hemoglobin [57]. Similarly, Nyagolov and colleagues also observed that the administration of melatonin (0.2 mg. kg) reduced aPTT and increased the activity of plasma clotting factors V, XII, and VIII, while luzindole (0.4 mg/kg) reduced these effects [58]. Obayashi and colleagues also reported a significant inverse association between urinary 6-sulfatoxymelatonin with platelet and white blood cell counts in a cohort of elderly Japanese participants [59].

The administration of melatonin (10 mg/kg, intraperitoneal injection) at 3, 8 and 16 h after injury to Wistar rats subjected to burns resulted in the decreased fibrin degradation products (24 h after), lengthened PT (3 and 24 h after), and increased glutathione (GSH; 3 and 24 h after). Decreased lipid peroxidation was also prominent 24 h after melatonin treatment which may be attributed to the anti-oxidative properties of melatonin or the elevation of GSH level [60]. In a study with a similar design, Bekyarova and colleagues administered 10 mg/kg melatonin immediately and 12 h after burning injury and observed inhibited prothrombin activity, reduced CRP, fibrinogen, and MDA levels, as well as normalizing platelet levels [61]. A study on diabetic rats also reported that the administration of melatonin results in prolonged bleeding time, prothrombin time, partial thromboplastin time, and inhibited platelet aggregation [62]. Calcium is the critical ion in the aggregation and activation of platelets. A study by Kumari and Dash, compared intracellular free $Ca^{2+}$ levels in controls with melatonin (100 or 500 μM) treated platelets. They reported that incubation with 500 μM of melatonin was associated with a significant elevation in the intracellular calcium levels while potentiating the thrombin-induced calcium rise [63].

There is evidence of a possible dose-dependent inhibitory effect of melatonin on platelet activity. Vacas and colleagues observed an inverse pattern in platelet sensitivity to melatonin and peak melatonin values, as evidenced by inhibition of arachidonic acid-induced platelet aggregation. However, the sample size ($n = 5$) was small and the findings require confirmation. They had also established the presence of high-affinity binding sites for [3H]-melatonin on the platelet membrane [64].

Wang and colleagues performed a study to evaluate the impact of melatonin on endothelial function markers in rats. In this model, the animals after receiving 20 mg/kg melatonin were evaluated two weeks later through blood samples and dissection of the abdominal artery. The expression levels of melatonin, platelet endothelial cell adhesion molecule-1 (CD31), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelin-1 (ET-1) significantly decreased, while expression levels of endothelial nitric oxide synthase (eNOS), nuclear erythroid 2-related factor 2 (Nrf2), NAD (*P*)H quinone oxidoreductase 1 (NQO-1), catalytic glutamate-cysteine ligase (GCLC) and heme oxygenase-1 (HO-1) significantly increased. In an associated human double-blind investigation, the participants included smokers or non-smokers, received 3 mg/day of melatonin. In association with melatonin intake, the concentration of fibrinogen (Fbg) and free fatty acids (FFA) were depressed in smokers, along with the decreased expression of ICAM-1, VCAM-1 and ET-1 and elevated expression of Nrf2 and HO-1 [65].

The role of sphingolipids in coagulation has bee34n documented, with a direct effect on plasma clotting factors Va and Xa [66]. Relative to this, Brunkhorst and colleagues observed that light exposure was associated with increased sphingosine 1-phosphate (S1P d18:1) and sphinganine 1-phosphate (S1P d18:0) in mice. The plasma concentrations of S1P d18:1 and S1P d18:0 exhibited an inverse correlation with intraplatelet values, which may be related to the involvement of sphingolipid signaling in platelet metabolism. These changes were not detectable in melatonin receptor-1/2 double knockout mice (MT1/2-/-) and melatonin deficient C57BL/6J mice. However, it is essential to note that no diurnal variation was present in sphingolipid-binding proteins or intraplatelet sphingolipid sources [67].

Findings from a cohort study showed that the administration of a single dose (3 mg) of melatonin to healthy young men ($n = 21$) resulted in a marked decrease in serum factor VIII, fibrinogen and D-dimer levels one hour after administration, when compared to controls [68]. The administration of melatonin to mice is associated with the inhibition of platelet activation by means of restoring peroxisome proliferator-activated receptor γ (PPARγ), resulting in the inhibition FUN14 domain containing 1 (FUNDC1)-dependent mitophagy and platelet hyperactivity [69]. Moreover, Girish and colleagues observed a significant increase in platelet apoptosis after melatonin administration, which was assumed to be a result of the elevation of intracellular calcium and ROS levels released from the mitochondria. Such effects, which may lead to thrombocytopenia, prompted the question of the safety of melatonin administration without further cautionary assessment. Iversen and colleagues also concluded that melatonin administration (2 mg per night; 4 doses) resulted in a decreased peak thrombin generation in tetraplegic patients compared to healthy controls receiving placebo. In a report on hemorrhagic stroke patients, the administration of melatonin (30 mg/d; 5 days) resulted in a significant decline in prothrombin time, fibrinogen levels, and factors VII and VWB [70].

The plasma concentration of tissue factor pathway inhibitor type 1 (TFPI-1)-free antigen has been reported to exhibit a circadian variation in healthy participants, but not in tetraplegic subjects; TFPI-1 is produced in vascular endothelium abrogates the extrinsic pathway of coagulation by directly inhibiting coagulation factor Xa and activated factor VII (FVIIa)–tissue factor (TF) complex [71]. An opposite rhythm has been reported relative to the plasma concentrations of TFPI-free antigen and melatonin in healthy participants, but not within the tetraplegic individuals. Tetraplegia interrupts the innervation to the pineal

gland such that the gland is no longer capable of melatonin production [55]. Kostovski and colleagues observed that the administration of melatonin promotes the release of TFPI from the endothelium, which contributes to the inhibition of coagulation [72]. Furthermore, melatonin administration (20 mg/d; one month) increases platelet count in patients with persistent thrombocytopenia [73]. A case series of 3 patients with idiopathic thrombocytopenic purpura garnered similar results with similar doses [74]. Such effects may result from the accelerated formation of colony-forming unit-megakaryocyte (CFU-MK), with larger megakaryocytes and the inhibition of serum-free-induced apoptosis in these cells via the activation of AKT/ERK signaling [75].

## 5. Melatonin in combination with anticoagulant drugs (heparin, warfarin): a promising future

Melatonin may be beneficial for the management of patients with coronary artery disease (CAD) due to the anti-inflammatory, antioxidant, and anti-thrombotic properties [76–78]. In this context, some laboratory experiments have shown that platelet aggregation is suppressed in response to melatonin [79,80]. In a placebo-controlled study, oral administration of the melatonin dose-dependently reduced coagulation activity in healthy young males. In fact, this study demonstrated that high concentrations of melatonin were correlated with lower levels of coagulation factors, namely fibrinogen and factor VIII activity [81]. In a pilot study performed on the interaction of melatonin and warfarin, 10 adult patients with a mean age of 54 years were enrolled and referred to Massachusetts General Hospital (Boston, MA) between April 2011 and April 2012. They concurrently received melatonin and warfarin for 2–10 days. The results demonstrated while the dose of melatonin was constant in all patients, the serum levels of warfarin fluctuated (increased/ decreased) in some participants. During the concomitant usage of melatonin and warfarin, prothrombin time (PT) and the international normalized ratio (INR) were markedly elevated while no bleeding was reported in patients. The Drug Interaction Probability Scale (DIPS) indicated that two patients had doubtful drug interactions, two patients had probable drug interactions, and six patients had possible drug interactions. The serum levels of albumin and liver function tests (LFTs) were normal in most subjects. The authors concluded that the combined use of warfarin and melatonin leads to a change in PT and INR and influences the coagulation activity. They suggested that regular monitoring of PT and INR is recommended for those concurrently receiving both drugs [82].

## 6. Melatonin, as an anti-coagulant in Covid-19: mechanisms of actions

As an adjunctive therapy, melatonin has been reported to reduce

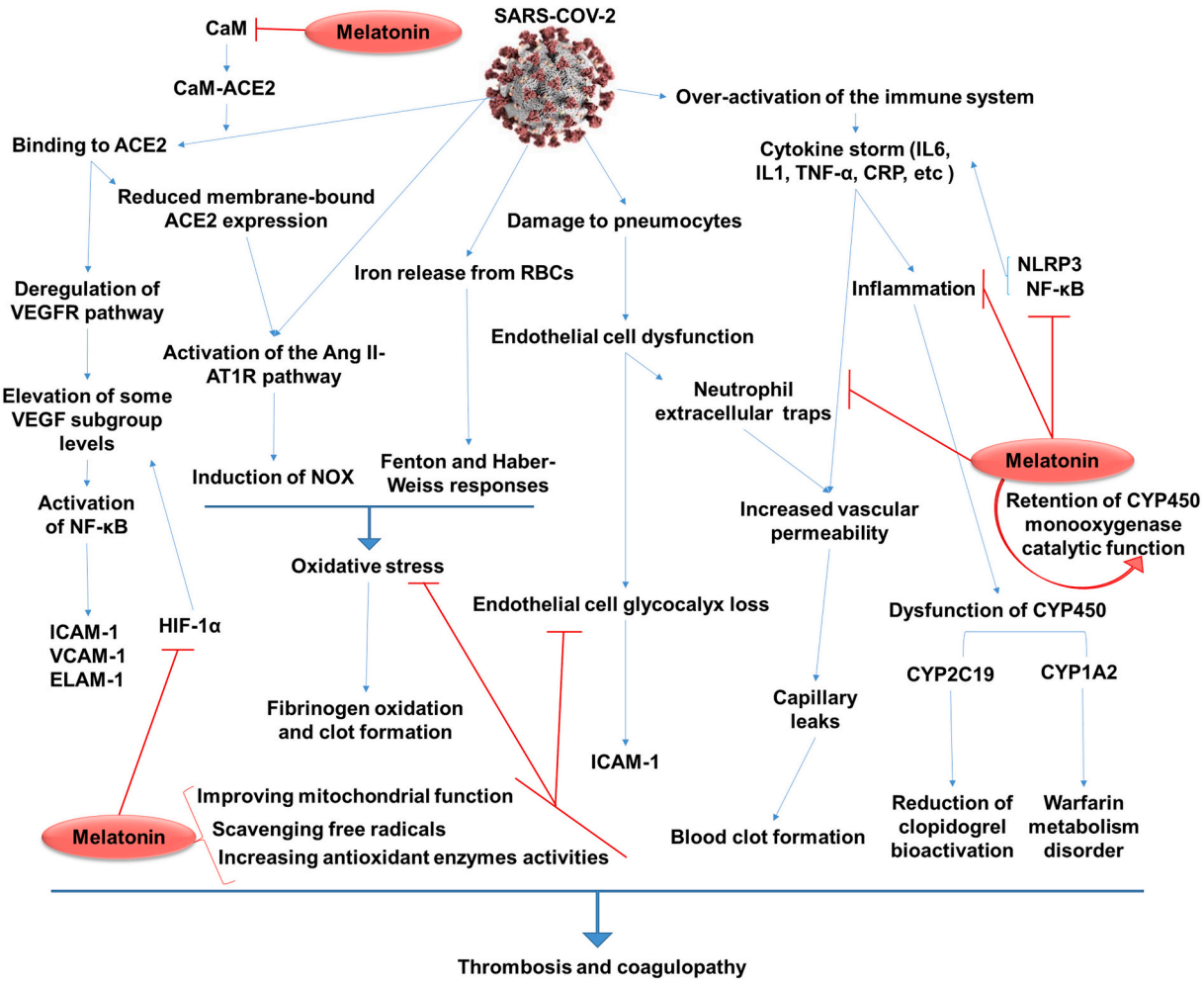


**Fig. 1.** Melatonin inhibits coagulopathy induced by SARS-CoV-2 infection through affecting various signaling pathways. ACE-2; angiotensin-converting enzyme-2, Ang II; angiotensin II, AT1R; Ang II receptor type 1, CYP450; cytochrome P450, HIF-1α; hypoxia-inducible factor 1-alpha, ELAM-1; endothelial-leukocyte adhesion molecule 1, ICAM-1; intercellular adhesion molecule 1, NF-κB; nuclear factor kappa B, NLRP3; NLR family pyrin domain containing 3, TNF-α; tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

thrombosis, sepsis and mortality rate in COVID-19 patients [83]. The effect of melatonin in the inhibition of SARS-CoV-2-induced coagulopathy may be mediated by impacting various cellular events (Fig. 1), which are described in following sections.

### 6.1. Cytochrome P450

Cytochrome P450 (CYP450) enzymes are a superfamily of phase I drug-metabolizing enzymes (DMEs) that play a crucial role in the biotransformation and pharmacokinetic conversion of therapeutic molecules, environmental toxins, and dietary supplements [84]; CYP3A4, CYP1A2, CYP2B6, CYP2C9, CYP2C19 and, CYP2D6 are the main known DMEs. Cytochrome P450 enzymes often catalyze various oxidative reactions, including hydroxylation, which prepares drugs for renal excretion [85]. Numerous clinical studies have investigated the role of CYP450 in the development of adverse drug reactions [84].

The activity of CYP450 is inhibited by inflammation in pre-and post-transcriptional pathways [86]. The inflammatory status of COVID-19, as well as the release of inflammatory cytokines such as IL-1, IFN, TNFα, and especially IL-6 are associated with decreased activity of drug-metabolizing enzymes and transporters [84,87]. As reported, CYP2C19 was associated with the largest decrease in its activity (75 %) after SARS-CoV-2 infection, which inversely associated with the elevation of IL-6, TNF-α, and CRP levels [86,88,89]. In a cohort study, CYP2C19 activity decreased by 57 % and was found to be negatively correlated with CRP levels [90]. Changes in CYP activity are significant in terms of adverse drug reactions; the ratio of the active metabolite of clopidogrel (bioactivated by CYP2C19) to clopidogrel in healthy individuals is 48 times higher than that of patients with Covid-19, and platelet aggregation is significantly higher in patients with elevated CRP levels [91,92]. In addition, during SARS-CoV-2 infection, CYP1A2 (warfarin as its substrate) activity decreases by 53 %, which is inversely related to IL-6 and CRP levels [86]. As a result, oral anticoagulants, which metabolized by CYP, should be used with caution because of the potential for unforeseen changes in drug metabolism in COVID-19 patients [93–95]. Furthermore, the activity of CYP2B6 and CYP2C9 increases, while the activity of CYP2D6 does not change in Covid-19 patients [86].

Melatonin has been reported to reduce the inflammatory mediators such as CRP, TNF-α and IL-6 levels, which indirectly regulate CYP levels [87]. On the other hand, melatonin is biotransformed by the CYP450 system. In addition to its role in melatonin catabolism, the CYP450 system is one of the principal sources of ROS generation in the cells [96–98]. Oxidative circumstances may change the biological activity of endoplasmic reticulum biomolecules, including phospholipids and enzymatic systems involved in drug biotransformation [99]. Melatonin has a potential role to retain the properties of CYP450 monooxygenase spectrum. Melatonin not only scavenges oxygen free radicals, but also protects the CYP450-catalyzed *O*-demethylation of p-nitroanisole from oxidative damage caused by $Fe^{3+}$/ascorbate. In its modified $Fe^{3+}$/ascorbate form, melatonin seems to bind to a critical histidine residue in the CYP450 monooxygenase, thereby protecting this enzyme and the CYP450 system's catalytic function; the cationic radical generated by the melatonin oxidation directly binds to nucleophilic sites of CYP450 such as those found in histidine residues and protect CYP450 from oxidative stress [100].

### 6.2. Cytokine storm and inflammation

Over-activation of the immune system results in a severe consequence known as cytokine storm or cytokine release syndrome (CRS), an uncontrolled production of pro-inflammatory cytokines and inflammatory cells leading to hyperinflammation [87]. Cytokine storm is critical in the progression of SARS-CoV-2 infection, leading to comorbidity in COVID-19 patients. The most prevalent co-morbidities linked with the COVID-19 are coagulopathy, thrombosis, and pulmonary problems [101]. Pro-inflammatory cytokines including IL-1, IL-2R, IL-6, and TNF-α are the key contributors to the cytokine storm [102]. The number of different inflammatory cells rises due to the cytokine storm. These cells produce cytokines attracting immune cells into the infection site, and at the same time, cytokines leave the bloodstream to enter the infected cells. As a result of these cellular activities, blood vessels become thinner and more permeable. The unregulated cycle of this process raises vascular permeability and ultimately leads to capillary leaks throughout the body. Excessive leakage of blood plasma into nearby cells forms a blood clot within the blood vessels, eventually causing coagulation and thrombosis [102,103].

Several investigations have indicated that melatonin can reduce inflammation in vivo and in vitro via regulating both pro-and anti-inflammatory cytokines in distinct pathophysiological situations [104–108]. Melatonin has been demonstrated to inhibit the expression of positive acute-phase proteins (APPs), pro-inflammatory cytokines, and chemokines such as IL-1, IL-6, TNF-, CCL2, CCL5, C-reactive protein, serum amyloid A, haptoglobin, ceruloplasmin, granulocyte monocyte colony-stimulating factor (GM-CSF), and − 1 antitrypsin. Furthermore, melatonin therapy increases the expression of the anti-inflammatory cytokine IL-1R and the negative APP fibrinogen [105]. Moreover, melatonin may reduce LPS-induced iNOS production by acting on nuclear factor kappa B (NF-κB) in rat endothelial cells and aortic rings. Activation of NF-κB pathway leads to the initiation of a cascade of molecular processes, some of which may be prospective targets for the treatment of inflammation. Melatonin performs part of its anti-inflammatory effect by altering nuclear NF-κB trafficking [104,109,110]. Furthermore, melatonin has an inhibitory effect on NLRP3 inflammation. In LPS-induced acute lung injury in mice, melatonin reduces the migration of neutrophils and macrophages into the lungs and limits lung damage through inhibiting NLRP3 inflammation [111]. Furthermore, melatonin ameliorates LPS-induced inflammation in rat adipose tissue by affecting the expression of inflammatory genes such as NLRP3 and ASC, leading to the reduction of caspase-1 and IL-1β expressions [112]; this results in the inhibition of {Liu, 2017 #52} pyroptosis, a type of programmed necrotic cell death induced by caspase-1 [112,113].

### 6.3. Oxidative stress

Oxidative stress is considered a significant factor in the progression of COVID-19 [114,115]. Evidence suggests that following activation of the Angiotensin (Ang) II -Ang II receptor type 1 (AT1R) pathway, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is activated [56,116–119]. NOX is present in many different cells and organs, like cardiomyocytes, vascular smooth muscle cells, endothelial cells, macrophages, and neutrophils [120], and its activation is one of the critical factors to the generation of reactive oxygen species (ROS) [121]. Studies have shown that COVID-19 patients experienced oxidative stress due to the activation of NOX [122] and inhibition of NOX-2 in macrophages has been reported to improve disease phenotypes by decreasing oxidative stress [123]. The activity of NOX may increase in the endothelial cells in response to the cytokines and other agonists [124], leading to the local oxidative stress and subsequent endothelial dysfunction [125]. Moreover, reduction of eNOS activity induces oxidative stress in SARS-CoV-2 infection [126].

Another mechanism in COVID-19 is the release of iron from red blood cells into the bloodstream, which can mediate Fenton and Haber-Weiss responses to induce oxidative stress. SARS-CoV-2 attacks hemoglobin [127] groups in red blood cells and releases free Fe (III) ions from the heme groups into the circulation [128], resulting in elevated ferritin levels [129]. Viral hemoglobinopathy and iron dysmetabolism may contribute to clinical pathologies such as oxidative stress, ferroptosis, lipid peroxidation, and mitochondrial damage [130]. In COVID-19 patients, oxidative stress may cause fibrinogen oxidation and clot formation, leading to coagulopathy [131]. Moreover, a higher neutrophils-to-

lymphocytes (N/L) ratio is identified in patients with COVID-19 [88], which is associated with an increased level of oxidative stress [132]; a higher N/L ratio increases the severity and mortality in COVID-19 cases [133,134].

Melatonin is a molecule with antioxidant properties and both scavenges free radicals and increases the expression and the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) by increasing their expression [135]. Melatonin is found on the cell membranes surface, near the polar heads of phospholipids, which protects cell membranes from oxidation through eliminating radicals before they harm cell membrane lipids and proteins by modifying the fluidity of the membranes [135]. Melatonin metabolites such as cyclic-3-hydroxymelatonin (c3OHM), N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuramine (AMK) are produced when it scavenges free radicals. These metabolites also have antioxidant properties and trap hydroxyl radicals and other ROS [25]. Furthermore, melatonin has an important role in boosting mitochondrial function by increasing complex I and complex IV activity and suppressing electron leakage [127].

### 6.4. Endothelial dysfunction

Endothelial cell dysfunction may occur following SARS-CoV-2 infection-induced damage to pneumocytes, resulting in aberrant coagulation and immunothrombosis [136,137], which suggest a bad prognosis in COVID-19 patients [102]. Spike protein of SARS-CoV-2 has been reported to bind to angiotensin-converting enzyme 2 (ACE2), leading to the degradation of the vascular endothelial growth factor (VEGF)-VEGF receptor (VEGFR) pathway and inhibition of VEGF activation; this is associated with the elevation of some VEGF subgroup levels, as key determinants for thrombosis and coagulopathy development [138]. Toll-like receptors, which are the predominant factors involved in inflammation and multiple pathologies in COVID-19 patients, are also highly expressed in endothelial cells; activation of these receptors enhances the release of inflammatory cytokines and proangiogenic agents (e.g., VEGF) which impact target organs [139,140]. VEGF induces the expression of endothelial cell adhesion molecules [e.g., ICAM-1, VCAM-1, and endothelial-leukocyte adhesion molecule 1 (ELAM-1)] during the inflammation via the activation of NF-κB pathway [140]. The effect of melatonin on the expression of VEGF has been widely studied. Melatonin prevents proliferation, invasion, and migration of human umbilical vein endothelial cells (HUVEC) by inhibiting VEGF activity [141,142]. Likewise, melatonin protects hypoxic brain endothelial cells from oxygen and glucose starvation through suppressing the expression of VEGF [44]. In addition, melatonin as a hypoxia-inducible factor 1-alpha (HIF-1α) inhibitor reduces VEGF expression in lung tissue of animals exposed to hypoxia [143]. Thus, due to the excessive level of VEGF in COVID-19 patients and the increased risk of endothelial dysfunction and clot formation, melatonin may have a beneficial effect in this regard [144].

Another proposed mechanism, which results in the endothelial dysfunction, are alterations in the function of the intact glycocalyx, a polysaccharide network which acts as a barrier against platelets and leukocytes [145–148]. Glycocalyx, composed of proteoglycans and glycoproteins, regulates the coagulation cascade by attaching to a cell membrane and maintaining membrane integrity by coating adhesion molecules ICAM-1. In this condition, the endothelial cell glycocalyx loss might contribute to the disruption of vascular homeostasis, resulting in endothelial dysfunction [145–149]. Investigations into the development of glycocalyx restoration and maintenance have been done and melatonin seems to be effective in the regeneration of the glycocalyx. Tunac and colleagues demonstrated that melatonin, as a result of its antioxidant activity, may reduce the ROS formation and protect glycocalyx by enhancing the activity of antioxidant enzymes [150]. Torres and colleagues reported that betahydroxybutyrate combined with melatonin (BHB/M) restored the glycocalyx layer to a baseline condition in male rats; this suggests the ability of melatonin in the protection of glycocalyx [151].

Neutrophil extracellular traps (NETs) are also altered in severe COVID-19 patients, suggesting a correlation with hypercoagulation activities. NETs are DNA, histone, and granular protein complexes released by active neutrophils; NETs are engaged in pathological processes such as coagulation problems and thrombosis, in addition to their critical function in the innate neutrophil immune response [152]. NETs modify endothelial barrier structure and increase vascular endothelial permeability, thereby reducing antithrombotic and anti-inflammatory properties [153,154]. Melatonin inhibits hyper-adhesiveness of endothelial cells induced by leukotriene B4-activated neutrophils, which results in the reduction in vascular permeability in rodents [155]. Furthermore, in humans, an inverse relationship exists between melatonin and the level of procoagulant factors including FVIII:C and fibrinogen [81].

### 6.5. ACE receptors

SARS-CoV-2 penetrates host cells an interaction of its spike protein with the ACE2 receptor [156]. The virus attaches to ACE2 through the S1 subunit of the S protein, whereas the S2 subunit is essential for viral fusion into the cell membrane [157]. The ACE2 enzyme, a homolog of ACE, is a crucial component of the renin-angiotensin system, which has the opposite action of ACE. The renin-angiotensin system has two pathways. The first pathway, which includes the ACE/ Ang II/ AT1R, raises ROS levels and impairs endothelial function and microcirculation. The ACE2/Ang receptor [1–7]/ mitochondrial assembly (MAS) receptor pathway is the second pathway [158]. Vasodilation, anti-inflammatory and anti-fibrotic actions result from biding of Ang 1–7 to the MAS receptor [159,160].

The ACE2/Ang receptor [1–7]/Mas receptor pathway inhibits the action of the ACE/Ang II/AT1R axis; this results in the reduction in inflammation and dilation of blood vessels [161]. The ACE2 enzyme malfunction causes aberrant activation of the ACE/Ang II/AT1R axis, which promotes platelet adhesion and accumulation, raising the risk of thromboembolism in many organs such as lungs, brain, heart, and kidneys [158]. The binding of SARS-CoV-2 to ACE2 and the endocytosis of viral particles by the ACE2 complex result in a reduction in membrane-bound ACE2 expression. Clinical studies demonstrate that reduced ACE2 expression shifts the renin–angiotensin system (RAS) balance toward the ACE/Ang II/AT1 pathway, which is implicated in organ damage. These findings imply that restoring tissue ACE2 levels and keeping the RAS balance from promoting the ACE/Ang II/AT1 pathway may be beneficial in treating COVID-19 patients. Accordingly, several experimental studies have shown the modulatory effects of melatonin on the RAS system [159].

Calmodulin (CaM) is a primary regulator of $Ca^{2+}$-dependent signaling in all eukaryotic cells [162]. Calmodulin is also involved in the regulation of ACE2 surface expression and retention in plasma membranes [39]. As a CaM inhibitor, melatonin boosts the ACE2 ectodomain release and reduces CaM-ACE2 interaction in a dose- and time-dependent manner [162,163]. As a result of this interaction, melatonin can be considered an indirect inhibitor of protein–protein interactions between ACE2-CoV2 during viral particle fusion [164].

## 7. Conclusions and perspective

Coagulopathy, thrombotic complications, and pulmonary problems are the most prevalent co-morbidities linked with COVID-19. Therefore, early detection of elevated coagulation biomarkers and therapeutic interventions could be beneficial for the management of patients with COVID-19. This review summarizes the consequences of SARS-CoV-2 infection on the activity and function of coagulation factors. The regulatory effect of melatonin on coagulation cascade parameters suggests that this molecule likely would protect COVID-19 patients against virus-induced coagulopathy and subsequent complications. Additional studies

are needed to further clarify melatonin's effects on signaling pathways regulating the coagulation machinery, which is impaired by SARS-CoV-2 infection. This review will hopefully stimulate additional research related to the impact of melatonin on COVID-19-induced coagulopathy.

## CRediT authorship contribution statement

**Azam Hosseinzadeh**: Conceptualization and Writing, **Abolfazl Bagherifard:** Writing- Original draft preparation, **Fereshteh Koosha:** Writing, **Shiva Amiri:** Gathering content and Writing, **Arman Karimi-Behnagh:** Gathering content and Writing, **Russel J Reiter:** Reviewing and Editing, **Saeed Mehrzadi***:* Supervision.

## Declaration of competing interest

None declared.

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