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Review Article

Zinc (II)-Induced Anti-Thrombus Formation against Severe COVID-19 Infection

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Zinc(II) induced neurological COVID-19 anti-thrombus formation has been established by that zinc induced inhibitive bronchial thrombosis and modulatory pulmonary thromboembolism are attained, causing COVID-19 activated anti-thrombus activity and leading to COVID-19 anti-thrombus formation. Zinc supplementation affected bronchial mucosal epithelial integrity, both under normal and zinc deficient conditions that there was an interaction between the individual zinc status. The other, zinc ions inhibit COVID-19 lung inflammation and promote platelet activation function that inhibits pulmonary thromboembolism, in which platelets could respond to changes in extracellular and intracellular Zn^{2+} concentration. Zinc-induced platelet aggregation, low concentrations of $ZnSO_4$ and zinc chelation involve platelet activation and potentiated platelet aggregation, in which Zn^{2+} plays a major role in the regulation of coagulation that zinc inhibit blood coagulation against COVID-19 infection. Zn^{2+} can modulate platelet and coagulation activation pathways, including fibrin formation that the release of ionic Zn^{2+} store contributes to the procoagulant role of Zn^{2+} in platelet-dependent fibrin formation. Further, zinc may reduce neurological resultings in COVID-19 patients that Zn^{2+} promotes inflammatory cytokine as a neurodegenerative disorder and the coronaviruses can affect the nervous system through blood circulation, causing neuro-inflammation. Zinc ions can inhibit inflammation, platelet behaviour function, and blood coagulation. Hence, zinc ions promote neurological anti-thrombosis formation during ROS production and excessive oxidative stress against COVID-19 infection. Persistent zinc intake for severe aggravation of COVID-19 has been suggested to be 8–11 mg/day for adults (upper intake level 40 mg/day) and suggesting that a zinc intake of 30–70 mg/day might aid in the RNA virus control. Accordingly, Zn^{2+} ions-binding molecular mechanism has been clarified that Zn^{2+} ions may be bound with COVID-19 inflammatory, platelet, coagulation, and thrombus various proteins by Zn^{2+} ions-centered tetrahedrally binding protein molecular coordination pattern.

Keywords: Zn^{2+} ion, Neurology in COVID-19 infection, Lung inflammation, Platelet activation, Blood coagulation, Thromboembolism, Zn^{2+} ions-centered coordinated binding proteins.

INTRODUCTION

SARS-CoV-2 or COVID-19 and SARS-CoV-2 RNA mutant virus pandemics have been increasingly developed and especially, the coronavirus pneumonia (COVID-19) has rapidly spread on a worldwide level. Epidemiological and clinical characteristics for rapid aggravated disease against severe SARS-CoV-2 or acute COVID-19 infection are involved with bronchitis difficulty due to bronchial thrombosis, viral pneumonia with virus spreading and inflammation, and thrombus formation and growth by blood coagulation.

Zinc as thrombus formation inhibitors are involved that zinc ions-mediated ACE2 activation may promote anti-thrombotic activity. SARS-CoV-2 RNA binds platelet ACE2 to promote thrombus formation. Spike protein recombinant human ACE2 protein and anti-spike monoclonal antibody could inhibit SARS-CoV-2 spike protein-induced platelet activation [1].

The immune characteristic of severe COVID-19 infection may be initiated by a particularly pro-inflammatory form of apoptosis with rapid viral replication leading to massive release of inflammatory

mediators, which resulting in thrombus formation and eventually death [2]. Microvascular thrombosis in lung capillaries is common in cute (adult) respiratory distress syndrome (ARDS) and is particularly prominent in COVID-19 pneumonia [3]. COVID-19 thrombosis features are expressed as venous thromboem-bolism (VTE) included pulmonary embolism (PE) and deep vein thrombosis (DVT), in which the main characteristics of VTE in COVID-19 are the capacity to affect all in-hospital patients, regardless of intensive care unit (ICU) or non-ICU stay [4]. Since approximately one-fourth of patients admitted to the ICU setting developed VTE, careful monitoring of the patients for VTE and its complications is strongly advised. The optimization of anticoagulant dosing to prevent VTE is currently under investigation. Thus, thrombosis process becomes underlying that COVID19-associated coagulopathy seems to join SARS-CoV-2 RNA virus to spike protein ACE2 receptor, endotheall injury, abnormal blood flow, platelet activation, platelet-derived thrombin, and immuno-thrombosis [5]. COVID-19 infection results thrombosis of comsumption coagulopathy that progression of inflammation mediated hemostasis dysregulation to thrombotic outcomes leads cause of abnormal coagulopathy [6]. In addition, an association between COVID-19 Infection and the occurrence of neurological disorders in neurolysis procceses is particulaly noteworthy for severe COVID-19 complicate patients [7]. Thrombus formation process consists complicatedly of possessing numerous aspects and mechanisms of coagulation, blood cllotting factor, platelet activation and aggregation, and embolization [8].

On the other hand, zinc is an important trace element for immune cells and important enzymes that 0.01-0.1 mM Zn^{2+} induced significant reductions of clotting times in a concentration-dependent manner. The procoagulant effect of Zn^{2+} occurred in the presence of Ca^{2+} but was inhibited by metal chelating agents. Higher levels of Zn^{2+} (> 0.2 mM final concentration) were required to accelerate thrombin-induced clot formation in the presence of citrate or oxalate. Similarly with oxalated human plasma, > 0.2 mM Zn^{2+} decreased the clotting time [9]. Further, zinc-induced neurological promotive anti-thrombosis as neurobiology frontier that Zinc-induced thrombus research had been carried out that lower zinc concentration (0.1 to 0.3 mmol/l) induces aggregation of washed platelet suspensions and higher concentrations (1 to 3 mmol/l) of zinc were needed to aggregate platelets in platelet-rich plasma obtained from blood anticoagulated with low-molecular-weight heparin. The outcomes have been obtained that zinc increases the rate of thrombin-induced fibrin clot formation and inhibits thrombin inhibition by antithrombin, and that zinc plays an important role in hemostasis, platelet aggregation, thrombosis, and atherosclerosis [10]. Zinc is involved in blood clot formation that there is a lot of evidence linking zinc to blood clotting. Zinc is released from cells called platelets that control blood clotting, and unwanted blood clots can form when zinc levels in the blood are faulty. It is unclear whether zinc inhibits VTE including pulmonary PE and DVT. Thus, zinc is involved in blood clot formation that there is a lot of evidence linking zinc to blood clotting.

In this review article, zinc (II) induced COVID-19 bronchial and pulmatory thrombus during thrombus process and ROS generation is discussed under inflammatory, platelet behaviour, coagulation, subsequently the zinc-binding ptoteins molecular mechanism is clarified.

Thrombus process in COVID-19 infection

COVID-19 thrombus process may consist of inflammatory activation, cytokine production, coagulation, thrombin generation, fibrin deposition, and blood clotty formation that a thrombus occurs when the hemostatic process, which normally occurs in response to injury, becomes activated in an uninjured or slightly injured vessel. A thrombus in a large blood vessel will decrease blood flow through that vessel (termed a mural thrombus) [11]. Hence, COVID-19 thrombus process is involved with the coagulation and the thromboembolism. The coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, whereas abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations [12]. Further, COVID-19 may contribute to venous thromboembolism (VTE) and result in immunothrombosis of COVID-19 [13]. The COVID-19-associated coagulopathy (CAC) and thrombosis have been resolved by the approaches that can induce the release of platelets and their activation and aggregation, and the generation of CAC also promotes coagulation [14].

Thus, COVID-19 thrombus process consists of inflammation, platelet function, blood coagulation, and thrombus formation.

Zinc induced COVID-19 neurological anti-thrombus activity in nervous system

COVID-19 thrombosis is of particular importance to the neurologist. Cardiovascular diseases (CVD) is the leading cause of neurological comorbidity in COVID-19. Furthermore, venous thromboembolism (VTE) is a leading complication of most neurological conditions. In the COVID-19 thrombosis, (1) Widespread activation of this 'thromboinflammatory' response can result in sepsis induced coagulopathy, multi organ dysfunction, (2) SARS-CoV-2 can invade vascular endothelial cells, causing the loss of the normal anticoagulant function of the endothelium, (3) Loss of anticoagulant function combines with platelet hyperactivity, enhanced leucocyte tissue factor expression and complement activation release of

neutrophil extracellular traps associated with the proinflammatory state in COVID-19 patients [15]. COVID-19 in neurological disorders can present with a large increase in systemic pro-inflammatory cytokines as a neurodegenerative disorder that cause neuroinflammation [16].

Zinc ion concentration is average 10 mg/g (wet weight) for mammal brain and roughly amounts to 0.15 mM for the blood serum and in extracellula fluid. In zinc nervous system, zinc deficiency results in behavioral symptoms, such as memory problems, malaise, or higher susceptibility to stress. Zinc in excess or deficit will cause pathological conditions that toxic levels of zinc have been shown to induce lethargy, neurotoxicity, and gliotoxicity, and high levels of zinc causes neuronal death in cortical cell tissue culture [17]. Hence, an excess of free zinc is detrimental and can lead to neuronal death. Zinc induced COVID-19 neurological anti-thrombus has been established by that zinc may promote COVID-19 neurological anti-thrombus, zinc dyshomeostasis may also be a hallmark of ageing and several neurological disorders [18], Zinc may promote inflammatory cytokine storms and the coronaviruses can affect the nervous system through blood circulation and cause neuroinflammation [16].

Zinc ions prevent respiratory thrombosis and pulmonary thromboembolism in COVID-19 infection

Zinc can prevent COVID-19 thrombosis that the contribution of extracellular or intracellular Zn^{2+} to megakaryocyte and platelet function and dysregulated Zn^{2+} homeostasis in platelet-related diseases by focusing on thrombosis, ischemic stroke and storage pool diseases. Consequently, zinc ions can impair the coagulation pathway and fibrin clot formation in humans, which can be more critical in patients with combined defects of both α and δ-granules or with thrombocytopenia [19]. The role of thrombosis in the disease process of COVID-19 contributes to the morbidity and mortality of infected patients. While manifestation of VTE and arterial thrombosis in the neurovascular system is recognized.

The effectiveness of zinc intake in preventing or treating SARS-CoV-2 infections is considered that the daily recommended dietary intake (RDI) of elemental zinc is around 2 mg for infants up to 6 months of age and gradually increases to 11 mg for males and 8 mg for females older than 13 years. Tolerable upper limits for zinc are estimated to be 7 mg for children aged 1–3 years of age, increas-ing up to 25 mg for adults and females of any age who are pregnant or lactating. The no observed adverse effect level (NOAEL) for adults is around 50 mg/day [20].

Zinc plays a complex role in haemostatic modulation acting as an effector of coagulation, anticoagulation and fibrinolysis. The defense on the severe bronchitis patients infected with SARS-CoV, MERS-CoV and SARS-CoV-2 has clinical features range from mild respiratory illness to severe acute respiratory disease. Both MERS and SARS patients in later stages develop respiratory distress and renal failure. The pneumonia appears to be the most frequent manifestation of SARS-CoV-2 infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging that the period from infection to appearance of symptoms varies [21].

Thromboembolism prevention is necessary that the neurovascular and cardiovascular systems as thromboembolic phenomenon suggest different pathophysiology of damage [22]. Zinc lozenges with a daily dose of >75 mg of zinc may shorten the duration of the common cold. A daily dose higher than 100 mg of elemental zinc in a lozenge is probably not advisable, as it is questionable whether there are any additional therapeutic effects. In adults, doses up to the NOAEL of 50 mg/ day should be considered for the prevention of SARS-CoV-2 or other viral respiratory infections [23].

Thus, zinc (by using 30～50～75 mg/day-zinc lozenges or 0.01-0.2 mmol/L solution Zn^{2+}) could prevent COVID-19 respiratory and pulmatotry thrombus formations.

Zinc ions inhibits COVID-19 respiratory thrombus formation

SARS-CoV-2 enters the target cells through the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease, serine 2 (TMPRSS2). The TMPRSS2 inhibitors block the cellular entry of the SARS-CoV-2 virus through the downregulated priming of the SARS-CoV-2 spike protein [24]. The other, zinc used as anti-inflammatory agent inhibits transient receptor potential vanilloid 1 (TRPV1) to alleviate neuropathic pain [25] that TRPV1 might decrease the severity of the acute respiratory distress syndrome present in COVID-19 patients [26].

COVID-19 respiratory system disorders such as respiratory tract epithelium, alveolar epithelium and interstitium, vascular endothelium, and excessive respiratory drive could lead to venous thromboembolic disease and pulmonary microvascular thrombosis [27]. Zinc could decrease thrombus formation in a clinical context that zinc supplementation of the zinc deficient diet group affected the integrity of the bronchial epithelium was shown by the number and length of cilia, and the number of epithelial cells [28].

Thus, COVID-19 respiratory system disorders such as respiratory tract epithelium, alveolar epithelium and interstitium, vascular endothelium, and excessive respiratory drive could lead to venous thromboembolic disease and pulmonary microvascular thrombosis.

Zinc ions modulate pulmonary thromboembolism against COVID-19 infection

The role of ACE2 in multiple organ damage caused by COVID-19 and SARS-CoV, targeted blocking drugs against ACE2, and drugs that inhibit inflammation in order to provide the basis for subsequent related research, diagnosis and treatment [29]. Zinc induced ACE2 activation promotes activity of anti-thrombus formation and growth against COVID-19 infection. Zinc activates COVID-19 ACE2 as entry receptor that zinc induced ACE2 activation promotes the activity of anti-thrombus formation growth, in which ACE2 activation decreases thrombus formation and reduces platelet attachment to vessels [30]. Further, treatment of zinc supplement for cardiovascular diseases (CVD) and COVID-19 comorbidity should be treat preventing viral replication by inhibiting the RNA-Dependent RNA Polymerase (RdRp) of the SARS-CoV-2, and enhance protective immune responses, and restoring functional balance of ACE2 [31].

Zinc ions is a platelet agonist that zinc-induced platelet aggregation involves secondary mediators of platelet activation and low concentrations of $ZnSO_4$ potentiated platelet aggregation by collagen-related peptide (CRP-XL), thrombin and adrenaline. Chelation of intracellular zinc reduced platelet aggregation induced by a number of different agonists, inhibited zinc-induced tyrosine phospho-rylation and inhibited platelet activation in whole blood under physiologically relevant flow conditions [32]. The other, although low serum zinc levels in critically ill patients infected by SARS-CoV-2, empirical zinc replacement should be avoided because of the risk of high-level toxicity (zinc levels ≥120 μg/dL), namely, for serum zinc level=70 (low level)～120 (high level) μg/dl, and low zinc levels were established if zinc levels were <70 μg/dL. COVID-19 patients showed significantly lower zinc levels when compared to healthy controls: median 74.5 (interquartile range 53.4–94.6) mg/dl vs 105.8 (interquartile range 95.65– 120.90) mg/dl. Amongst the COVID-19 patients, 27 (57.4%) were found to be zinc deficient. These patients were found to have higher rates of complications, acute respiratory distress syndrome, corticosteroid therapy, prolonged hospital stay, and increased mortality. The odds ratio (OR) of developing complications was 5.54 for zinc deficient COVID-19 patients [33, 34].

The potential role of zinc as an adjuvant therapy for SARS-CoV-2 may be broader than just antiviral and/or immunological support. Zinc also plays a complex role in haemostatic modulation acting as an effector of coagulation, anticoagulation and fibrinolysis [35]. Zinc is an important cofactor in haemostasis and thrombosis that zinc compounds such as anti-coagulant [36], blood clotting [37], and thrombotic complication [38] can promote subsets of the reactions of the contact pathway, with implications for a variety of disease states and prove useful in preventing thrombosis and the formation of obstructive clots.

SARS-CoV-2 can cause mild respiratory infections or severe acute respiratory syndrome with consequent inflammatory responses that considering inflammation plays a significant role in COVID-19 pathology. Anti-inflammatory treatments may hold promise for the management of COVID-19 complications [39]. However, the role of zinc in regulation of inflammatory response and pneumonia pathogenesis are important that zinc ions may inhibit COVID-19 lung inflammation. Zn^{2+} ions may possess anti-inflammatory effects in pneumonia with limiting tissue damage and systemic effects.

How anti-coagulation that occlusive pulmonary embolism (PE) strongly support a hypercoagulable state incurred by SARS-CoV-2 and the medical community to share a perspective about long-term management guidelines for SARS-CoV-2 associated venous thromboembolism (VTE) and prompt future research [40]. The presence of lung thrombosis seems a universally recognized feature of COVID-19 disease whether these thrombi can resolve in response to anticoagulant therapy is still matter of debate. Transient clinical improvement upon treatment with high dose of anti-coagulants could be observed within an old, organized thrombus detached from the arterial wall, consistent with re-canalization of the vessel [41]. Zinc ions promote platelet activation function and inhibit pulmonary thromboembolism, in which the influence of Zn^{2+} on platelet behaviour during thrombus formation and the contributions of exogenous and intracellular Zn^{2+} to platelet function have been evaluated having the mechanisms by which platelets could respond to changes in extracellular and intracellular Zn^{2+} concentration [42]. Zn^{2+} accelerates clot formation by enhancing fibrin assembly, resulting in increased fibre thickness that Zn^{2+} promotes clotting and reduces fibrin clot stiffness in a Factor XIII or fibrin stabilizing factor (FXIII)-independent manner, suggesting that zinc may work in concert with FXIII to modulate clot strength and stability [43]. Zn^{2+}-induced platelet activation is integrin aIIbb3-dependent that integrin αIIbβ3 is expressed at a high level in platelets and their progenitors, where it plays a central role in platelet functions, hemostasis, and arterial thrombosis. Zinc ions promote platelet activation that Zn^{2+}-induced platelet activation contributes to the procoagulant role in platelet-dependent fibrin formation, and leading to modulation of thrombosis formation [44]. Thus, zinc regulates coagulation, platelet aggregation, anticoagulation and fibrinolysis and outlines how zinc serves as a ubiquitous modulator of haemostasis and thrombosis.

Zinc inhibit blood coagulation against COVID-19 infection, activated platelets secrete zinc into the local microenvironment, the concentration of

zinc increases in the vicinity of a thrombus. Consequently, the role of zinc varies depending on the microenviron-ment of a feature that endows zinc with the capacity to spatially and temporally regulate haemostasis and thrombosis [45].

Zn^{2+} also circulates at a concentration of 10–20 μM in the blood plasma. Zn^{2+} can modulate platelet and coagulation activation pathways, including fibrin formation that the release of ionic Zn^{2+} store from secretory granules upon platelet activation contributes to the procoagulant role of Zn^{2+} in platelet-dependent fibrin formation [46]. Zn^{2+} ions-induced platelet activation, blood coagulation, and thrombosis formation are mediated that persistent zinc ion concentration for aggravated COVID-19 patient is involved that zinc intake for severe aggravation of COVID-19 suggesting that the recommended daily allowance (RDA) of zinc according to the Dietary Recommendation Intake (DRI), is 8–11 mg/day for adults (tolerable upper intake level 40 mg/day) and that a zinc intake of 30–70 mg/day might aid in the COVID-19 RNA virus control [47]. Thus, 50 mg Zn/day caused a factor to increased platelet reactivity, which could cause a predisposition to increased coagulability [48].

Zinc induced COVID-19 also neurological anti-thrombosis with acute neurologic infectious patients is involed that neurological COVID-19 acute ischemic stroke in thrombus process occurs in a higher probability of early mortality and zinc ions-induced activated anti-thrombus activity is proceeded to support an ideal medical treatment regimen for patients presenting with acute ischemic stroke or to prevent acute ischemic stroke among hospitalized COVID-19 patients. Patients with COVID-19 were experiencing acute ischemic stroke in spite of therapeutic anticoagulation [49]. Thus, it is thought that zinc ions-induced effects to severe COVID-19 neurological anti-thrombosis may become effective also against a soften nervous system.

Accordingly, COVID-19 ACE2 is an integral membrane-bound zinc-metallopeptidase that zinc ions can inhibit inflammation, platelet behaviour function, blood coagulation, and thrombosis formation against COVID-19 infection. Zinc influences thrombocyte aggregation and coagulation, indicating that zinc could decrease thrombus formation. In addition, COVID-19 mutation also possesses a high thrombophilic risk, but zinc ions could inhibit the coagulation and the thrombus formation [50]. The Zn^{2+} ions-binding molecular mechanism is considered that zinc ions may be bound by zinc ions centered tetrahedrally binding proteins molecular coordination.

Zinc induced ROS generation in COVID-19 infection

In COVID−19 infections, the large artery inflammation secondary to the cytokine storm results in the formation of unlimited quantities of reactive oxygen species (ROS) produced through activation of the mitochondrial respiratory chain, peroxisomal fatty acid metabolism, and flavoprotein oxidases. In addition, COVID-19 infection is associated with the generation of interleukins and tumor necrosis factor (TNF α), which increase neutrophil myeloperoxidase (MPO) activity. Excessive MPO activity can generate the Fenton reaction to further produce ROS that including the highly reactive hydroxyl radical (•OH), superoxide ($O_2•^-$) and hydrogen peroxide MPO-H_2O_2 [51]. Oxidative stress by ROS is related to all the main changes observed in other inflammatory and infectious diseases. The host's response to viral infection emphasizes oxidative stress rather than the virus's mechanisms of aggression [52].

The high neutrophil to lymphocyte ratio observed in critically ill patients with COVID-19 is associated with excessive levels of ROS, which promote a cascade of biological events that drive pathological host responses. ROS induce tissue damage, thrombosis and red blood cell (RBC) dysfunction, which contribute to COVID-19 disease severity. Free radical scavengers could be beneficial for the most vulnerable patients. Excessive oxidative stress might be responsible for the alveolar damage, thrombosis and RBC dysregulation seen in COVID-19. Anti-oxidants and elastase inhibitors may have therapeutic potential [53].

ROS are involved in the regulation of all of the major processes that promote the formation of venous thrombi. Oxidative stress also appears to control the remodeling of a venous thrombus and adjacent vein wall including fibrinolysis, sterile inflammation, extracellular matrix deposition and its remodeling, and neovascularization [54]. DVT formation and resolution are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, as well as platelets, endothelial cells, neutrophils, monocytes and fibroblasts. Functional controlling with Zn^{2+} ions and ROS production in platelets could inhibit thrombus formation [55]. Zinc could decrease thrombus formation in a clinical context. Complications of SARS-CoV2 infections also include tissue damage affecting the gastrointestinal system, the liver, kidneys, blood vessels. Balanced zinc homeostasis is essential for tissue recovery after mechanical and inflammation-mediated damage, adding more potential benefits of zinc supplemen-tation of COVID-19 patients. Antioxidant treatments can abolish the possible participation of ROS generated by thrombosis in neutrophils activated by the COVID–19 infection [56]. Thus, zinc influences thrombocyte aggregation, coagulation, and thrombosis.

As mentioned above, zinc (II) ions-induced anti-inflammation, platelet activation, aggregation,

blood anti-coagulation, and reducing neurological thrombotic formation during thrombus process and ROS production against severe COVID-19 infection are expressed in *Table 1*. *Accordingly*, zinc ions-binding molecular mechanism becomes clarified that zinc ions could be bound with inflammatory, thrombocytic, coagulative, and thrombotic proteins by Zn^{2+} ions-centered coordinated tetrahedrally binding proteins.

Table-1: Zn^{2+} ions-induced anti-inflammation, platelet activation, blood anti-coagulation, and reduced neurological anti-thrombus formation during thrombus process and ROS production against severe COVID-19 infection

Zn^{2+} ions	**Zn^{2+} induced COVID-19 anti-inflammation, anti-platelet function, anti-coagulation, blood cllotting, and neurological anti-thrombus formation during thrombus process and ROS production**			
Zn^{2+} →	**Anti-Inflammation**	**Platelet Behaviour**	**Anti-Coagulation**	**Anti-Thrombus Formation**
	→ Zn^{2+}, ROS	**→ Zn^{2+}, ROS**	**→ Zn^{2+}, ROS**	**→ Zn^{2+}, ROS**
	·TRPV1 decreases respiratory distress syndrome ·Regulation of inflammatory response. ·Inhibition of lung inflammation ·ROS in lung inflammation result oxidative stress	·Zinc-induced, $ZnSO_4$, Zn chelation promote platelet activation. ·ROS regulate platelet function ·Platelet-dependent fibrin formation.	·Anti-coagulation integrin aIIbb3-dependent. ·Zinc controls blood cllotting. ·ROS stimulate coagulation	·Zn^{2+}-induced platelet activation enhances anti-thrombus growth. ·ROS resolve venous thrombus ·Zinc promotes COVID-19 reduced neurologi-cal anti-thrombosis and anti-ischemic stroke
	Zinc ions-binding molecular mechanism: Zinc ions can be bound with inflammatory, thrombocytic, coagulative, and thrombotic various proteins by Zn^{2+} ions-centered coordinated tetrahedrally binding proteins.			

CONCLUSIONS

Zn^{2+} ions-induced neurological COVID-19 inhibitive respiratory thrombosis and modulatory acute pulmonary thromboembolism during thrombus process and ROS production have been established, leading to anti-thrombus formation, subsequently zinc binding molecular mechanism is clarified.

Zinc induced COVID-19 ACE2 activation as entry receptor promotes activity of anti-thrombus formation and growth that the ACE2 activation decreases thrombus formation and reduces platelet attachment to vessels. Thrombus process becomes underlying that COVID19-associated coagulopathy seems to join SARS-CoV-2 RNA virus to spike protein ACE2 receptor, abnormal blood flow, platelet activation, platelet-derived thrombin, and immunothrombosis. Zinc can inhibit inflammation, platelet behaviour function, blood coagulation, and thrombus formation against COVID-19 infection. Zinc ions could decrease thrombus formation that zinc supplementation of the zinc deficient diet group affected the integrity of the bronchial epithelium, in which was shown by the number and length of cilia, and the number of epithelial cells and zinc supplementation affected bronchial mucosal epithelial integrity, both under normal and zinc deficient conditions that there was an interaction between the individual zinc status and zinc supplementation in terms of the number of bronchial mucosal epithelial cells. An excess of free zinc is detrimental and can lead to neuronal death.

The other, zinc ions promote platelet activation function and modulate pulmonary thromboembolism, in which the influence of Zn^{2+} on platelet behaviour during thrombus formation and the contributions of exogenous and intracellular Zn^{2+} to platelet function are evaluated having the mechanisms by which platelets could respond to changes in extracellular and intracellular Zn^{2+} concentration.

Zn^{2+}-induced platelet activation is integrin aIIbb3-dependent. Zn^{2+} plays a major role in the regulation of coagulation that zinc inhibit blood coagulation against COVID-19 infection that Zn^{2+} can modulate platelet and coagulation activation pathways, including fibrin formation that the release of ionic Zn^{2+} store from secretory granules upon platelet activation contributes to the procoagulant role of Zn^{2+} in platelet-dependent fibrin formation.

Further, zinc induced COVID-19 neurological anti-thrombus has been established by that zinc may promote COVID-19 neurological anti-thrombosis. Neurological COVID-19 acute ischemic stroke in thrombus process occurs in a higher probability of early

mortality and zinc ions-induced activated anti-thrombus activity is proceeded to support an ideal medical treatment regimen for patients presenting with acute ischemic stroke or to prevent acute ischemic stroke among hospitalized COVID-19 patients.

Zinc induced lung inflammatory ROS productions lead to that especially, ROS induce tissue damage, thrombosis and RBC dysfunction, which contribute to COVID-19 disease severity that free radical scavengers could be beneficial for the most vulnerable patients. Excessive oxidative stress might be responsible for the alveolar damage, thrombosis and RBC dysregulation seen in COVID-19.

Persistent zinc intake for severe aggravation of COVID-19 has suggested that RDA is 8–11 mg/day for adults (tolerable upper intake level 40 mg/day), suggesting that a zinc intake of 30–70 mg/day might aid in the RNA viruses control. Thus, zinc ions can inhibit inflammation, platelet behaviour function, blood coagulation that zinc ions promote neurological anti-thrombosis formation during ROS production, excessive oxidative stress, and thrombus process against COVID-19 infection.

Accordingly, zinc ions-binding molecular mechanism has been clarified that Zn^{2+} ions may be bound with COVID-19 inflammatory, platelet, coagulation, thrombus various proteins by Zn^{2+} ions-centered tetrahedrally binding protein molecules coordination pattern.

ABBREVIATIONS

ACE2=angiotensin-converting enzyme 2. **ARDS=**acute (adult) respiratory distress syndrome, **ATE=**arterial thromboembolism, **CAC=**COVID-19-associated coagulopathy, **COVID-19=**coronavirus disease-2019, **COVID AtoZ=**COVID-19, Using Ascorbic Acid and Zinc Supplementation, **CRP=**collagen-related peptide, **CUS=** compression ultrasound, **CVD=**cardiovascular diseases, **DRI=**dietary reference intake, **DVT=**deep vein thrombosis, **ER=** endoplasmatic reticulum, **ICU=**intensive care unit, **MPO=** myeloperoxidase, **NIH=**National Institutes of Health, **NOAEL=**no observed adverse effect level, **PE=**pulmonary embolism, **RDA=**recommended daily allowance, **RDI=**recommended dietary intake, **RBC=**red blood cell, **RdRp=**RNA-dependent RNA Polymerase, **ROS=**reactive oxygen species, **SARS=**severe acute respiratory syndrome coronavirus 2, **TMPRSS2=**transmembrane serine protease 2, **TNF=**tumor necrosis factor, **TRPV1=**transient receptor potential vanilloid 1, **VTE=**venous thromboembolism,

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