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Review Article

Zinc(II)-Induced Immunological COVID-19 Suppressive Bronchitis Thrombosis and Neurological COVID-19 Modulatory Pulmonary Thromboembolism: A Semi-Review

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Abstract

Zinc(II) induced immunological COVID-19 suppressive bronchial thrombosis and neurological COVID-19 modulatory pulmonary thromboembolism during thrombus process have been established by that Zn^{2+} ions suppress respiratory thrombosis and modulate pulmonary thromboembolism during thrombus process and ROS generation, leading to the anti-thrombus formation against severe COVID-19 infection.

Zinc supplementation affected immunological 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. The other, Zn^{2+} can modulate neurological platelet and coagulation activation pathways that inhibits pulmonary thromboembolism, in which platelets could respond to changes in extracellular and intracellular Zn^{2+} concent-ration. Zinc ions inhibit COVID-19 lung inflammation. 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 inhibits blood coagulation against COVID-19 infection.

Further, zinc may reduce neurological resulting 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 promote neurological anti-thrombus formation during ROS production and excessive oxidative stress against COVID-19 infection. Thus, zinc ions can inhibit inflammation, platelet behavior function, and blood coagulation.

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 bronchial, pulmonary, inflammatory, platelet, coagulation, thrombus various proteins by Zn^{2+} ions-centered tetrahedrally binding protein molecular coordination pattern, leading that zinc induced suppression of respiratory thtrombosis and modulation of pulmonary thromboembolism enhance anti-thrombus formations.

Keywords

Zn^{2+} ion; COVID-19 lung Inflammation; Platelet Activation; Blood Coagulation; Thrombosis and Thromboembolism; Zn^{2+} ions-Centered Coordinated Binding Proteins.

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2; ARDS: Acute (Adult) Respiratory Distress Syndrome; ATE: Arterial Thromboembolism; CAC: COVID-19-Associated Coagulopathy; CF: Cystic Fibrosis; COPD: Chronic Obstructive Pulmonary Diseases; COVID-19: Coronavirus Disease-2019; COVID AtoZ: COVID-19 A to Z; 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: Endoplasmic Reticulum; ICU: Intensive Care Unit; MPO: Myeloperoxidase; NIH: National Institutes of Health, NK: Natural Killer; NOAEL: No Observed Adverse Effect Level; PE: Pulmonary Embolism, PTE: Pulmonary Thromboembolism; 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,

Introduction

COVID-19 RNA mutant virus pandemics have been increasingly developed and especially, the coronavirus pneumonia (COVID-19) has rapidly spread on a worldwide level. Clinical characteristics for 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. The immune characteristic of severe COVID-19 infection may be initiated by a pro-inflammatory form of apoptosis with rapid viral replication leading to massive release of inflammatory mediators, which resulting in thrombus formation and eventually death [1]. Microvascular thrombosis in lung capillaries is common in cute (adult) respiratory distress syndrome (ARDS) and is particularly prominent in COVID-19 pneumonia [2]. COVID-19 thrombosis features are expressed as venous thromboembolism (VTE) included pulmonary embolism (PE) and deep vein thrombosis (DVT) [3]. COVID-19 infection results thrombosis of comsumption coagulo-pathy that progression of inflammation mediated hemostasis dysregulation to thrombotic outcomes leads cause of abnormal coagulopathy [4]. Thrombus formation process consists complicatedly of possessing numerous aspects and mechanisms of coagulation, blood cllotting factor, platelet activation and aggregation, and embolization [5].

While, 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 [6]. Zinc as thrombus formation inhibitors is 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 [7].

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. 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 [8].

Thus, 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.

In this review article, zinc (II) - induced suppressive bronchial thrombus and modulatory pulmonary thromboembolism are discussed immunologically and neurologically under the thrombus process and ROS production against severe COVID-19 infection, subsequent to the zinc-binding proteins molecular mechanism is clarified.

Zinc induced immunological COVID-19 thrombosis in nervous system

Zinc having susceptibility and adequate immunity for COVID-19 needs balanced zinc levels that zinc levels cause impairment of a destructive function of macrophages and overload of regulatory T–cells that may harm the immune function as well [9]. Zinc has favourable impacts on adaptive and innate immune cells and enhances their growth, development, and function, and zinc decreases inflammatory cytokines that are important in severe lung inflammation. Zinc is responsible for the secretion of pro-inflammatory cytokines and it suppresses inflammation by inhibition of leukocyte function-associated antigen-1 [10]. Zinc balancing power regarding immune cell numbers and functions might be highly beneficial in regard to therapy of COVID-19 that for a physiological inflammatory response and phagocytic activity macrophages need sufficient intracellular zinc levels.

In addition, for natural killer (NK) cells and cytotoxic T cells, zinc supplementation increased their cytotoxicity toward target cells with zinc balancing at Zinc acetate 20 mg/day, Zinc gluconate 10 mg/day, Zinc gluconate 30 mg/day (elemental) [11].

COVID-19 thrombosis is of particular importance to the neurologist. Cardiovascular diseases (CVD) and venous thromboembolism (VTE) are the leading cause of neurological comorbidity in COVID-19 and a leading complication of most neurological conditions. In the COVID-19 thrombosis, (1) thromboinflammatory response can result in sepsis induced coagulopathy, (2) COVID-19 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 [12]. Zinc may promote inflammatory cytokine storms and the coronaviruses can affect the nervous system through blood circulation and COVID-19 in neurological disorders can present with a large increase in systemic pro-inflammatory cytokines as a neurodegenerative disorder that cause neuroinflammation [13]. 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 [14]. An excess of free zinc is detrimental and can lead to neuronal death.

Thus, 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 [15].

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) [16]. 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 [17]. Further, COVID-19 may contribute to venous thromboembolism (VTE) and result in immunothrombosis of COVID-19 [18]. 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 [19].

Zinc(II) ions induced immunological COVID-19 preventions for respiratory thrombosis and pulmonary thromboembolism

Homeostasis of zinc in human body is highly controlled with zinc-mediated modulation of immune function that zinc facilitates transduction of a various signalling cascades in reaction to stimuli received from extra cellular environment. The maximum amount of zinc ingestion for children and adult men is valuating at 0.023-0.028 g a day along with 45 mg a day in each case. A normal zinc accumulation during pregnancy periods is 0.73 mg a day. The absorption of zinc in pregnant and non-pregnant women is the same, but about 2.35 mg/day absorption has been utilized to estimate the additional requirement of pregnant women [20]. Zinc immune balance that maintaining adequate zinc balance is important to protect from microorganisms, including viral infections that zinc balance might enhance the host response and be protective of viral infections with the tolerable upper intake level for zinc 40 mg/day [21].

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, increasing 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 [22]. 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 [23]. 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 [24]. 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. Thromboembolism prevention is necessary that the neurovascular and cardiovascular systems as thromboembolic phenomenon suggest different pathophysiology of damage [25].

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 [26].

In addition, arterial thrombosis such as compensatory hypertrophy of bronchial arteries occurs in atherosclerotic plaque rupture, as a result of clot formation of chronic pulmonary thromboembolism (PTE) and pulmonary, leading to platelet aggregation, thrombus formation and vessel occlusion [27]. This bronchial artery thromboembolism against COVID-19 is thought to be prevented or modulated with potential role of zinc ions-binding thrombus-forming proteins [28].

Zn^{2+} ions suppress COVID-19 bronchial thrombosis

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 [29]. The other, zinc used as anti-inflammatory agent inhibits transient receptor potential vanilloid 1 (TRPV1) to alleviate neuropathic pain that TRPV1 might decrease the severity of the acute respiratory distress syndrome present in COVID-19 patients [30, 31]. 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 [32]. 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 [33].

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

Zn^{2+} ions modulate severe COVID-19 neurological pulmonary thromboembolism

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 [34]. 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 [35]. 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 [36]. 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 [37].

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 [38, 39].

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 [40]. Zinc is an important cofactor in haemostasis and thrombosis that zinc compounds such as anti-coagulant blood clotting and thrombotic complication 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 [41-43].

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 [44]. 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 [45]. 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 [46]. Zinc ions promote platelet activation function and inhibit pulmonary thromboembolism, in which the influence of Zn^{2+} on platelet behavior 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 [47]. 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 [48]. Zn^{2+}-induced platelet activation contributes to the procoagulant role in platelet-dependent fibrin formation, and leading to modulation of thrombosis formation [49]. 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 [50]. Thus, zinc regulates coagulation, platelet aggregation, anticoagulation and fibrinolysis and outlines how zinc serves as a ubiquitous modulator of haemostasis and thrombosis.

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 [51]. 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 [52]. Thus, 50 mg Zn/day caused a factor to increased platelet reactivity, which could cause a predisposition to increased coagulability [53].

Zinc induced COVID-19 also neurological anti-thrombosis with acute neurologic infectious patients is involved that zinc ions-induced effects to severe COVID-19 neurological anti-thrombosis may become effective also against a soften nervous system [54].

In addition, clinical trials that study zinc supplementation in lung disease are carried out that zinc supplements (50 mg/day), zinc acetate (20 mg/day), zinc (30 mg/day), and zinc tablets (30 mg/day) have been adapted to be applicable as new therapeutics under zinc homeostasis in lung inflammatory disorders such as asthma, chronic obstructive pulmonary diseases (COPD), and cystic fibrosis (CF) [55].

Accordingly, COVID-19 ACE2 is an integral membrane-bound zinc-metallopeptidase that zinc ions can inhibit inflammation, platelet behavior 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 [56].

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

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 [57].

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 [58]. 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 [59].

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 [60]. Functional controlling with Zn^{2+} ions and ROS production in platelets could inhibit thrombus formation [61].

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, and blood vessels. Balanced zinc homeostasis is essential for tissue recovery after mechanical and inflammation-mediated damage, adding more potential benefits of zinc supplementation of COVID-19 patients. Antioxidant treatments can abolish the possible participation of ROS generated by thrombosis in neutrophils activated by the COVID–19 infection [62]. Thus, zinc influences thrombocyte aggregation, coagulation, and thrombosis.

As mentioned above, zinc (II)-induced immunological COVID-19 suppressive bronchitis thrombosis and neurological COVID-19 modulatory pulmonary thromboembolism of anti-inflammation, virus entry inhibitor, respiratory system disorders, platelet activation, blood anti-coagulation, and reducing thrombotic formation during thrombus process and ROS production are represented in.

Accordingly, zinc ions-binding molecular mechanism becomes clarified that zinc ions could be bound with respiratory, pulmonary, inflammatory, thrombocytic, coagulative, and thrombotic much proteins by Zn^{2+} ions-centered coordinated tetrahedrally binding proteins (Table 1).

Zinc(II) - induced bindng molecular mechanism by Zn^{2+} induced suppressive respiratory thrombosis and modulatory pulmonary thromboembolism

Zinc ions suppress respirtory thrombosis and modulate pulmonary thromboembolism. The zinc binding molecular mechanism of the zinc-respiratory thrombosis and the zinc-pulmonary thromboembolism interactions should be elucidated infectious surface cell against COVID-19. The Zn^{2+} ions-various proteins complexes by coordinated binding model of zinc-ligands such as ligands of alanine, serine, histidine in many proteins are involved that the interactions of zinc-ions respiratory thrombosis and pulmonary thromboembolism had been found on the binding specificity by Zn^{2+} ions-centered tetrahedral geometric coordination of the inhibitors. The zinc-ions proteins complexes may play important role for this Zn^{2+} ions-centered coordination pattern that the zinc-coordinating inhibitor of tetrahedral zinc sites is tetrahedrally coordinated binding to such as the catalytic triad of zinc ions-various proteins intractions-mediated Serine, Histidine and Aspartate hydrogen residues of various proteins. Thus, molecular mechanism of zinc ions dependent much proteins is involved that Zn^{2+} induced respiratory thrombosis and pulmonary thromboembolism can contribute to the anti-thrombus formation.

Accordingly, the zinc binding molecular mehanism is clarified that the Zn^{2+} ions-proteins complexes formations by zinc ions-centered coordinated tetrahedrally binding with various proteins may be proceeded, resulting that zinc induced suppression of respiratory thtrombosis and modulation of pulmonary thromboembolism enhance anti-thrombus formations, in which the zinc-coordinating inhibitor of tetrahedral zinc sites is tetrahedrally coordinated binding to such as the catalytic triad of zinc-suppressive respiratory branchilis and zinc-pulmatory thromboembolism of zinc-mediated Alanine, Serine, Histidine and Aspartate hydrogen residues.

Conclusions

Zinc (II) - induced immune suppressive respiratory thrombosis and neurological modulatory pulmonary thromboembolism during thrombus

Table 1: Zinc(Ⅱ)-induced COVID-19 immunological suppressive bronchial thrombosis and COVID-19 neurological modulatory pulmonary thromboembolism of anti-inflammation, platelet activation, anti-coagulation, and reducing thrombotic formation during thrombus process and ROS production

Zn^{2+} ions	Zn^{2+}induced immune COVID-19 suppressive bronchial thrombosis and neurological COVID-19 modulatory pulmonary thromboembolism of anti-inflammation, anti-platelet function, anti- coagulation, and anti-thrombus formation during thrombus process and ROS production					
	Immunological COVID-19 Suppressive Bronchitis Thrombosis			Neurological COVID-19 Modulatory Pulmonary Thromboembolism		
	Anti-Inflammation	Virus Entry Inhibitor	Respiratory System Disorders	Anti- Inflammation	Anti-Coagulation	Anti-Thrombus Formation
Zn^{2+} →	→ Zn^{2+}, ROS	→Zn^{2+}, ROS	→ Zn^{2+}, ROS	→Zn^{2+},ROS	→Zn^{2+}, ROS	→Zn^{2+}, ROS
	Bronchial thrombus and respiratory and inflammatory regulation of inflammatory response.	Zn-TMPRSS2 inhibitor blocks the cellular entry through the down regulated priming of the COVID-19 spike protein	Respiratory tract epithelium, alveolar epithelium and interstitial, vascular endothelium, and excessive respiratory drive could lead to venous thromboembolic disease	Inhibition of lung inflammation	Anti-coagulation integrin aIIbb3-dependent.	Zinc promotes COVID-19 reduced neurolo-gical anti-thrombosis and anti-ischemic stroke
	Tolerable upper intake level for zinc 40 mg/day	TRPV1 decreases the severity of the acute respiratory distress syndrome	ROS resolve venous thrombus	ROS in lung inflammation result oxidative stress	Zinc controls blood cllotting.	Zinc decreases thrombus formation
	Zinc 30～50 ～75 mg/day- zinc lozenges or 0.01-0.2 mmol /L solution Zn2+ could prevent COVID-19 respiratory and pulmatotry thrombus formations	Zinc immune balancing at Zinc acetate 20 mg/ day, Zinc gluconate 10 mg/day, Zinc gluconate 30 mg/day	Valuating at 0.023-0.028g a day along with 45 mg a day	Functional controlling with Zn2+ ions and ROS production in platelets could inhibit thrombus formation.	Zinc-induced, ZnSO4, Zn chelation promote platelet activation.	Zinc supplements (50mg/day), Zinc acetate (20mg/day), Zinc (30mg/day), and Zinc tablets (30 mg/day) have been adapted to be applicable as new therapeutics under zinc homeostasis in lung inflammatory disorders such as asthma, COPD.
			Zinc adequate immunity for COVID-19 needs balanced zinc levels	Zinc 30-50 mg/day could suppress lung inflammation	ROS stimulate coagulation	
					ROS regulate platelet function	
					Platelet depen-dent fibrin formation.	
					Zn2+ induced platelet activa-tion enhances anti-thrombus growth.	
	Zinc ions-binding molecular mechanism: Zinc ions can be bound with bronchitic, inflammatory, thrombocytic, coagulative, and thrombotic various proteins by Zn^{2+} ions-central coordinated tetrahedrally binding various proteins, leading the neurological anti-thrombus activity and anti-thrombus formation and growth.					

process have been established by which Zn^{2+} ions prevent immunological respiratory thrombosis and modulate neurological pulmonary thromboembolism in ROS productions during thrombus process, leading to the anti-thrombus formation in severe COVID-19 infection.

Zn^{2+} ions-induced neurological COVID-19 severe respiratory thrombosis and acute pulmonary thromboembolism during ROS production, haemostatis, and thrombus process have been discussed, and 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 thrombosis 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 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 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, the zinc binding molecular mehanism is clarified that the zinc-coordinating inhibitor of tetrahedral zinc sites is tetrahedrally coordinated binding to such as the catalytic triad of zinc-inhibitory respiratory branchilis and zinc-pulmatory thromboembolism of zinc-mediated Alanine, Serine, Histidine and Aspartate Hydrogen Residues.

Finally, the zinc binding molecular mehanism is involved that the Zn^{2+} ions-proteins complexes formations by zinc ions-centered coordinated tetrahedrally binding with various proteins may be proceeded during thrombus process, ROS production, and excessive oxidative stress, resulting that zinc induced suppression of respiratory thrombosis and modulation of pulmonary thromboembolism enhance anti-thrombus formations.

Conflicts of Interest

The author declares there is no conflicts of interest.

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