ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 5, Issue –3, June - 2020, Page No. : 526 - 534

Role of Oral Zinc Supplement in COVID-19

[1]Aditya K. Gautam, Assistant Professor in Departement of Respiratory Medicine, UPUMS, Saifai, Etawah, U.P. India
[2]Adesh Kumar, Professor & Head in Department of Respiratory Medicine, UPUMS, Saifai, Etawah, U.P. India
[3]Ashish K. Gupta, Associate Professor in Department of Respiratory Medicine, UPUMS, Saifai, Etawah, U.P. India
[4]Prashant Yadav, Assistant Professor in Department of Respiratory Medicine in UPUMS, Saifai, Etawah,U.P. India
Corresponding Author: Aditya K. Gautam, Assistant Professor in Departement of Respiratory Medicine, UPUMS, Saifai, Etawah, U.P. India

Citation this Article: Aditya K. Gautam,Adesh Kumar, Ashish K. Gupta,Prashant Yadav, "Role of Oral Zinc Supplement in COVID-19", IJMSIR- June - 2020, Vol – 5, Issue -3, P. No. 526 – 534.
Type of Publication: Review Article
Conflicts of Interest: Nil

Abstract

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) represents a global health challenge for the human beings. Till the moment, there is no definitive therapeutic strategies to deal with this disease, only supportive therapy is available all over world. The zinc (Zn) is well known to possesses a variety of direct and indirect antiviral properties, which are realized through different mechanisms. It also having the immune-booster property. Oral Zn supplement has a potential to enhance antiviral immunity, both innate and humoral, and to restore depleted immune cell function or to improve normal immune cell function.

Zn may also act in a synergistic manner when co-administered with the standard antiviral therapy, as was demonstrated in patients with influenza, RSV, H1N1, HIV, HCV and SARS-CoV. Effectiveness of Zn against a number of viral species is mainly realized through the physical processes, such as virus attachment, infection, and uncoating. Zn may blocking of the virus entry into the cell by protecting or stabilizing the cell membrane. On the other hand, it was also demonstrated in several studies that Zn may inhibit viral replication by alteration of the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase (RdRp) in rhinoviruses, HCV, influenza virus and SARS-CoV, and diminish the RNA-synthesizing activity of nidoviruses, from which SARS-CoV-2 belongs. Therefore, it may be hypothesized that Oral Zn supplement may have a potential role for prevention and treatment of COVID-19.

Keywords: COVID-19, Zn supplement, antiviral, immune-booster, prevention, treatment

Introduction

The 2019–2020 will be remembered for the global pandemic of the Coronavirus Disease 2019 (COVID-19), caused by Coronaviridae family—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, Hubei Province, China, and quickly spread globally due to its very high contagiousity, so the World Health Organization (WHO) declared

Coronavirus Disease 2019 (COVID-19) outbreak as pandemic on March 11, 2020.

SARS-CoV-2 primarily infects cells of the small air sacs known as alveoli consisting of alveolar cells and alveolar macrophages causes an inflammatory condition also known as pneumonia affecting primarily alveoli [1]. Typically, symptoms include a combination of non-productive or dry cough, chest pain, fever, and difficulty in breathing. The pneumonic condition in COVID-19 is severe and is associated with its high mortality.

In view of the emerging COVID-19 pandemic caused by SARS-CoV-2 virus, the search for potential protective and therapeutic antiviral treatment is of particular and urgent interest.Till the date no any specific treatment available for COVID-19.The role of immunomodulaters has been proven in many studies to supress the severity and duration of symptoms and play a protective role in many viral infections including COVID-19. Zinc is known to modulate antiviral and antibacterial immunity and regulate inflammatory response.

This review focuses on the role of zinc as an essential micronutrient that is required to mount an effective antiviral response. Although zinc possesses direct antiviral properties (e.g. influenza), it is also critical in generating both innate and acquired (humoral) antiviral responses. Zinc is an integral component of many viral enzymes, proteases, and polymerases, highlighting the importance of regulating cellular and systemic zinc distribution to inhibit viral replication and dissemination.

Zinc Supplement in viral infections

Many studies have evaluated the efficacy of zinc as an antiviral agent in vitro. Unfortunately, zinc concentrations used to assess antiviral activity often far exceed physiological concentrations. Human plasma zinc, for example, ranges from approximately 10 to 18 µM [2], whereas antiviral concentrations of zinc can reach into mM concentrations [3]. Intracellular zinc concentrations range from 10s to 100s of µM, but are significantly buffered by zinc-binding proteins such as metallothioneins, rendering free zinc concentrations at picomolar to low nanomolar concentrations [4,5]. The antiviral properties of zinc are certainly virus-specific, but it would appear that zinc ion availability plays a significant role in the antiviral efficacy of zinc [6].

Researchers have performed several studies testing whether zinc supplements can help treat or prevent the common cold.

A comprehensive review of 18 of these trials found that intake of zinc was associated with a reduction in the duration of patient's common cold symptoms, but not the severity. The chance of developing a cold, school absences and antibiotic prescription rates were also lower in the groups that took zinc, suggesting that it not only helps reduce the length of the cold but also prevents it.

The findings of this study weren't all good news, people that took zinc also reported more incidences of bad taste and nausea than people who took a placebo. Still, the science suggests that zinc supplements sound pretty helpful in treating the symptoms of the common cold.

Zinc oxide nanoparticles demonstrated promising antiviral effects against H1N1 influenza virus infection[7] .Zn may also efficiently inhibit membrane fusion of respiratory syncytial virus, HSV, Semliki Forest virus and sindbis viruses, which is realized through binding to a specific histidine residue revealed on the viral E1 protein at low endosomal pH [8]. Zn^{2+} have a potential for direct inactivation of the free Varicella-Zoster virus in vitro [9].

Few studies have examined the antiviral effects of zinc on some respiratory viruses. In vitro replication of influenza (PR/8/34) is significantly inhibited by the addition of the zinc ionophore pyrrolidine dithiocarbamate [10], perhaps through inhibition of the RNA-dependent RNA polymerase (RdRp), as had been suggested 30 y earlier [11]. In similar fashion, severe acute respiratory syndrome (SARS) coronavirus RdRp template binding and elongation was inhibited by zinc in Vero-E6 cells. Moreover, zinc salts were shown to inhibit respiratory syncytial virus, even while zinc was incubated with HEp-2 cells only before infection, and then removed [12]. The authors suggest that this indicates an inhibitory mechanism similar to HSV by preventing viral membrane fusion; however, no measures were taken to assess changes in intracellular zinc content, nor inhibition of other aspects of the viral life cycle.

Despite limited data on the direct effect of zinc on SARS-CoV-2, its antiviral effects were demonstrated in other viral diseases. Zinc was shown to have a significant impact on viral infections through modulation of viral particle entry, fusion, replication, viral protein translation and further release for a number of viruses including those involved in respiratory system pathology [13,14]. In addition, Zn treatment was shown to increase interferon α (IFNα) production by leukocytes [15] and potentiate its antiviral activity in rhinovirus-infected cells [16].

As antiviral activity of IFNα is mediated through JAk1/STAT1 downstream signaling and up-regulation of antiviral enzymes [e.g., latent ribonuclease (RNaseL) and protein kinase RNA-activated (PkR)] involved in viral RNA degradation and inhibition of viral RNA translation [17], recent findings allow to propose that these mechanisms may be stimulated by Zn2+. A systematic review by Singh and Das [18] published in Cochrane database revealed a significant reduction in common cold duration, as well as the incidence rate ratio of developing common cold (IRR=0.64 (95% cI: 0.47-0.88), P=0.006) in response to zinc supplementation. Certain studies also revealed the association between Zn status and respiratory syncytial virus (RSV) infection [19]. Zn compounds were shown to inhibit respiratory syncytial virus replication and RSV plaque formation with a more than 1,000-fold reduction at 10 μm Zn preincubation [20].

Role of Zinc in immunomodulation

Micronutrients including Zinc, in general, play an important role in maintaining adequate immune activity, and impairment of micronutrient balance adversely affects the immune system to increase the susceptibility to various bacterial and viral microorganisms. Zinc, in addition to being a cofactor to more than 300 enzymes[21], is essential for membrane integrity, DNA synthesis, and cell proliferation, and thus is needed for all highly proliferating cells, especially the immune cells[22].

Zinc has been shown to play an important role in the regulation of the immune response, particularly T cell-mediated function[23]. Similar to changes observed in the immune response of the elderly, zinc deficiency is associated with thymus involution and reductions in lymphocyte proliferation, decrease T helper cells and antibody response to vaccines[24]. Zinc deficiency in humans decreases the activity of serum thymulin (a thymic hormone), which is required for maturation of T-helper cells. T-helper 1 (Th(1)) cytokines are decreased but T-helper 2 (Th(2)) cytokines are not affected by zinc deficiency in humans. This shift of Th(1) to Th(2) function results in cell-mediated immune dysfunction. Because IL-2

production (Th(1) cytokine) is decreased, this leads to decreased activities of natural-killer cell and T cytolytic cells, which are involved in killing viruses, bacteria, and tumor cells[25]. Decreases, increases, or no changes in monocytes and neutrophils functions have been reported due to changes in zinc status[26]. In monocytes, all functions are impaired, whereas in natural killer cells, cytotoxicity is decreased, and in neutrophil granulocytes, phagocytosis is reduced[27]. Like the elderly, zinc-deficient subjects have greater susceptibility to a variety of pathogens[28].

Previous in vitro studies have demonstrated that Zn induces the production of IFN-α and IFN-γ and can potentiate the antiviral action of the former. Ex vivo experiments showed that Zn supplementation may improve leukocyte IFN-α production and reduce mononuclear cell tumor necrosis factor (TNF) production [29]. In healthy humans, Zn supplementation has also decreased the production of TNF-α and interleukin-1β[30]. Zn also enhances cell's resistance to apoptosis through inhibition of caspases-3, 6, and 9, and an increase of the Bcl-2/Bax ratio [31], and such antiapoptotic effects at both the peripheral and thymic level could result in an increase in the number of T helpers. Zn induced alteration of the capillary epithelium might inhibit transcapillary movement of plasma proteins and reduce local edema, inflammation, exudation, and mucus secretion [32]. Zn may also protect or stabilize the cell membrane which could contribute to an inhibition of the entry of the virus into the cell [33].

Zinc Supplement in SARS-CoV-2

SARS-CoV-2 is one of the seven types of corona virus that are known to infect humans. Based on the genetic properties coronaviruses are grouped into four genera: α-CoV, β-CoV, γ-CoV and δ-CoV and the COVID-19 belongs to β-CoV. Like other coronaviruses, SARS-CoV-2 is also an enveloped virus with a single-strand, positive-sense RNA genome [34].

Coronaviruses constitute the subfamily Orthocoronavirinae, within the family Coronaviridae, order Nidovirales, and realm Riboviria. Nidoviruses is a large group of positive-strand RNA (+RNA) viruses, which includes major pathogens of humans and livestock, such as SARS-CoV and other human coronaviruses, the arteriviruses (e.g., equine arteritis virus [EAV]), and porcine reproductive and respiratory syndrome virus (PRRSV) [35].

Zn effectively inhibits the RNA-synthesizing activity of nidoviruses (including SARS-CoV) in vitro, which is realized through alteration of RdRp (RNA dependent RNA polymerase) activity during the elongation phase of RNA synthesis, probably by directly affecting template binding [36].

Zn2+ cations especially in combination with Zn ionophore pyrithione were shown to inhibit SARS-coronavirus RNA polymerase (RNA dependent RNA polymerase, RdRp) activity by decreasing its replication [37]. Such an effect could be reversed by addition of a Zn2+ chelator (MgEDTA). An in vitro enzyme activity assay demonstrated inhibition of RNA synthesis of SARS-CoV, RdRp-RTCs (RNA-dependent RNA polymerase replication and transcription complex) with just zinc along with the removal of inhibition with the addition of MgEDTA, a zinc chelator [37]. Thus, it may be suggested that in coronaviruses, Zn2+ may inhibit both the proper proteolytic processing of replicase polyproteins and RdRp activity [36]. Of note, like other coronaviruses, SARS-CoV-2 causing COVID-19 also comes under nidovirus group. RdRp and 3CLpro protease of SARSCoV-2 share over 95% of sequence similarity

with those of SARS-CoV despite the fact that these two viruses demonstrate only 79% sequence similarity at the genome level [38]. It allows to hypothesize that antiviral effects of Zn may be realized in SARS-CoV-2 as well.

Another hypothesis that Zinc is considered as the potential supportive treatment in therapy of COVID-19 infection due to its immune modulatory effect, as well as direct antiviral effect [39]. We have discussed the immunomodulatory effect of zinc under the heading Role of Zinc in immunomodulation.

The oral mucosa and gastrointestinal tract have the highest expression of ACE2 and TMPRSS2 (transmembrane Serine Protease 2), which are required for SARS-CoV-2 infection. The ACE2 receptor is targeted by SARS-CoV-2 for entry into cells with help from TMPRSS2[40]. Furthermore, the oral mucosa and gastrointestinal tract are likely the first primary sites of SARS-CoV-2 infection . Therefore, one proposed mechanism of action for orally absorbed zinc is the inhibition of SARS-CoV-2 RdRp-RTCs in the oral mucosa and possibly the gastrointestinal tract in order to delay the spread of the infection to the lung epithelium.

A complementary mechanism is the inhibition of SARS-CoV-2 RdRp-RTCs in the lung epithelium with the help of a zinc ionophore. This line of reasoning provides a basis for why oral administration of zinc could be an effective treatment for reducing the severity of COVID-19.

The anti-malarial drug chloroquine and its metabolite hydroxychloroquine are currently being tested in several clinical trials as potential drugs to limit COVID-19 mediated morbidity and mortality. These drugs inhibit pH-dependent steps of COVID-19 replication by increasing pH in intracellular vesicles and interfere with virus particle delivery into host cells. Besides direct antiviral effects, these anti-malarial drugs specifically target extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and coronavirus replication.

As zinc deficiency is frequent in older adults and patients suffering from cardiovascular disease, chronic pulmonary disease, or diabetes, these drugs combined with zinc supplements can prove more effective in reducing COVID-19 morbidity and mortality than chloroquine or hydroxychloroquine individually [41]. Therefore, these anti-malarial drugs in combination with zinc should be considered for COVID-19 clinical trials.This support again the role of Zn supplement in COVID-19.

Conclusion

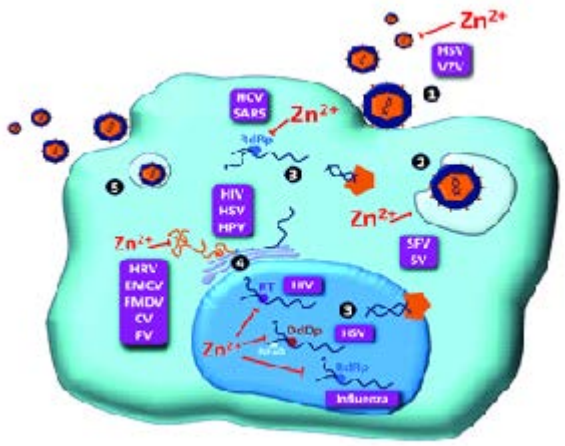
Although a variety of drugs and compound have been studied, a specific therapy is still lacking for the effective treatment of SARS-CoV-2. Zn executed its antiviral effects by generating both innate and acquired (humoral) immune responses, facilitation of the normal functioning of innate immune system, inhibiting the entry of the virus via stabilization of cell membrane, and inhibition of viral replication through interference with the viral genome transcription, protein translation, polyprotein processing, viral attachment, and uncoating (**Figure 1**).

RdRps are suitable targets for antiviral drug development as their activity is strictly virus-specific and may be blocked without severely affecting key cellular functions in nidovirus group from which SARS-CoV belong. RdRp and 3CLpro protease of SARSCoV-2 share over 95% of sequence similarity with those of SARS-CoV. Zinc also play a role in prevention of replication of RNA by inhibiting RdRp in

Nidovirus like SARS-CoV. Zn also increase the efficacy of chloroquine and hydroxychloroquine the drugs which used in treatment of COVID-19.Due to these property of Zinc it may be hypothesized that Zinc supplement may have a potential role in the treatment of COVID-19, although there is limited data regarding the definitive role of Zn in COVID-19.

It may also keep in mind that overdose of zinc may have many side effects like nausea, vomiting, abdominal pain, diarrhoea, copper deficiency, anemia and change in taste (metallic taste) etc. More importantly, consuming around 25-50 mg zinc per day is affordable, and less likely to induce human toxicity, as >200 to 400 mg per day of zinc consumption has shown to induce adverse effects [42]. In conclusion, maintaining adequate zinc balance is important to protect from microorganisms, including viral infections.

Summarizing the available information, consuming up to 50 mg of zinc per day might provide an additional shield against the COVID-19 pandemic, possibly by increasing the host resistance to viral infection to minimize the burden of the disease. In this pandemic situation, intensive clinical trials need to be conducted in order to develop an effective drug to treat the patients of COVID-19, till the time any effective vaccine is developed.



The diverse stages of viral replication cycles that are inhibited by zinc. In vitro studies have demonstrated a number of mechanisms by which zinc interferes with the viral replication cycle. These include free virus inactivation (1), inhibition of viral uncoating (2), viral genome transcription (3), and viral protein translation and polyprotein processing (4).

CV, coronavirus; DdDp, DNA-dependent DNA polymerase; EMCV, encephalomyocarditis virus; FMDV, foot and mouth disease virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HRV, human rhinovirus; HSV, herpes simplex virus; PV, polio virus; RdRp, RNA-dependent RNA polymerase; RT, reverse transcriptase; SARS, severe acute respiratory syndrome coronavirus; SFV, Semliki Forest virus; SV, sindbis virus; VZV, varicella-zoster virus; Zn, zinc.

Acknowledgments: The authors' responsibilities were as follows—corresponding author designed the review and performed the study selection, all authors read and approved the final paper.

References

1. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GFEpidemiology, genetic recombination, and pathogenesis of coronaviruses.Trends Microbiol. 2016; 24:490–502
2. Rukgauer M, Klein J, Kruse-Jarres JD. Reference values for the trace elements copper, manganese, selenium, and zinc in the serum/plasma of children, adolescents, and adults. J Trace Elem Med Biol. 1997;11(2):92–8.
3. Kumel G, Schrader S, Zentgraf H, Daus H, Brendel M. The mechanism of the antiherpetic activity of zinc-sulfate. J Gen Virol. 1990;71:2989–97.
4. Krezel A, Maret W. Zinc-buffering capacity of a eukaryotic cell at physiological pZn. J Biol Inorg Chem. 2006;11(8):1049–62.

5. Colvin RA, Bush AI, Volitakis I, Fontaine CP, Thomas D, Kikuchi K, Holmes WR. Insights into Zn2+ homeostasis in neurons from experimental and modeling studies. Am J Physiol Cell Physiol. 2008;294(3):C726–C42.
6. Eby GA. Zinc ion availability—the determinant of efficacy in zinc lozenge treatment of common colds. J Antimicrob Chemother. 1997;40(4):483–93.
7. H. Ghaffari, A. Tavakoli, A. Moradi, A. Tabarraei, F. Bokharaei-Salim, M. Zahmatkeshan, M. Farahmand, D. Javanmard, S.J. Kiani, M. Esghaei, V. PirhajatiMahabadi, S.H. Monavari, A. Ataei-Pirkooh, Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine, J Biomed Sci.2019;26: 70.
8. C.Y. Liu, M. Kielian.Identification of a specific region in the e1 fusion protein involved in zinc inhibition of semliki forest virus fusion J Virol.2012;86, pp. 3588-3594
9. S. Shishkov, T. Varadinova, P. Bontchev, C. Nachev, E. Michailova. Complexes of zinc with picolinic and aspartic acids inactivate free varicella-zoster virions Met Based Drugs.1996;3,pp.11-14
10. Uchide N, Ohyama K, Bessho T, Yuan B, Yamakawa T. Effect of antioxidants on apoptosis induced by influenza virus infection: inhibition of viral gene replication and transcription with pyrrolidine dithiocarbamate. Antiviral Res. 2002;56(3):207–17.
11. Oxford JS, Perrin DD. Inhibition of the particle-associated RNA-dependent RNA polymerase activity of influenza viruses by chelating agents. J Gen Virol. 1974;23(1):59–71.
12. Suara RO, Crowe JE Jr. Effect of zinc salts on respiratory syncytial virus replication. Antimicrob Agents Chemother. 2004;48(3):783–90.
13. Read SA, Obeid S, Ahlenstiel c and Ahlenstiel g: The role of zinc in antiviral immunity. Adv Nutr.2019; 10: 696-710
14. Ishida T: Review on the role of Zn2+ ions in viral pathogenesis and the effect of Zn2+ ions for host cell-virus growth inhibition. Am J Biomed Sci Res.2019; 2,AJBSR.MS.Id.000566.
15. Cakman I, Kirchner H and Rink L: Zinc supplementation reconstitutes the production of interferon-α by leukocytes from elderly persons. J Interferon cytokine Res.1997; 17: 469-472.
16. Berg k, Bolt g, Andersen H and Owen Tc: Zinc potentiates the antiviral action of human IFN-α tenfold. J Interferon cytokine Res.2001; 21: 471-474.
17. Lin Fc and Young HA: Interferons: Success in anti-viral immunotherapy. cytokine growth Factor Rev.2014; 25: 369-376.
18. Singh M and Das RR: Zinc for the common cold. cochrane database Syst Rev. 2013; cd001364.
19. Che Z and Sun J: Investigation on relationship between whole blood zinc and Fe elements with children pneumonia caused by respiratory syncytial virus. Int J Lab Med.2016; 37: 2401-2402.
20. Van der Gucht W, Leemans A, De Schryver M, Heykers A, Caljon G, Maes L, Cos P, Delputte PL.Virol J . Respiratory syncytial virus (RSV) entry is inhibited by serine protease inhibitor AEBSF when present during an early stage of infection. 2017 Aug 17;14(1):157.

21. Rink L, Kirchner H, Rink L, Kirchner H. Zinc-altered immune function and cytokine production. J Nutr. 2000;130(Suppl):S1407–S1411.
22. Fraker PJ, King LE, Laakko T, *et al*. The dynamic link between the integrity of the immune system and zinc status. J Nutr. 2000;130(Suppl):S1399–S1406.
23. Ibs KH, Rink L. Zinc-altered immune function. J Nutr. 2003;133 (Suppl):S1452–S1456.
24. Fraker PJ, King LE. Reprogramming of the immune system during zinc deficiency. Annu Rev Nutr. 2004;24:277–298.
25. Prasad AS. Zinc: mechanisms of host defense.J Nutr. 2007 May;137(5):1345-9.
26. Kruse-Jarres JD, Kruse-Jarres JD. The significance of zinc for humoral and cellular immunity. J Trace Elem Electrolytes Health Dis.1989;3:1–8.
27. Walker CF, Black RE. Zinc and the risk for infectious disease. Annu Rev Nutr. 2004;24:255–275.
28. Ibs KH, Rink L. Zinc-altered immune function. J Nutr. 2003;133(5 Suppl 1):1452S–6S.
29. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. J Interferon Cytokine Res. 1997;17:469–72.
30. Perry DK, Smyth MJ, Stennicke HR, et al. Zinc is a potent inhibitor of the apoptotic protease, caspase-3: a novel target for zinc in the inhibition of apoptosis. J Biol Chem. 1997;272:18530–3.
31. Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. Med Hypotheses. 1996;46:295–302.
32. Pasternak CA. A novel form of host defence: membrane protection by Ca2+ and Zn2+. Biosci Rep. 1987;7:81–91.
33. Forni D, Cagliani R, Clerici M, Sironi M. Molecular evolution of human coronavirus genomes. Trends Microbiol. 2017; 25:35–48.
34. Gorbalenya AE, Enjuanes L, Ziebuhr J, Snijder EJ. Nidovirales: evolving the largest RNA virus genome. Virus Res. 2006;117:17–37.
35. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009;7:439–50.
36. Te Velthuis AJ, van den Worm SH, Sims Ac, Baric RS, Snijder EJ and van Hemert MJ: Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog.2010; 6: e1001176.
37. Te Velthuis AJW, Van den Worm SHE, Sims AC, Baric RS, Snijder EJ, Van Hemert MJ. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010;6:e1001176.
38. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565–74.
39. Zhang L and Liu y: Potential interventions for novel coronavirus in china: A systematic review. J Med Virol.2020; 92: 479-490.
40. Hoffmann M, Kleine-Weber H, Krueger N, Mueller MA, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular

protease TMPRSS2 for entry into target cells. BioRxiv. 2020.

41. Dr. Soumitra Das. Zinc can play pertinent role in mitigating COVID-19. ET Health World.May 07,2020.
42. G.J. Fosmire, Zinc toxicity, Am J Clin Nutr.1990;51:225-227.