Zinc and SARS-CoV-2: A molecular modeling study of Zn interactions with RNA-dependent RNA-polymerase and 3C-like proteinase enzymes

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Received May 27, 2020; Accepted October 13, 2020

DOI: 10.3892/ijmm.2020.4790

Abstract. RNA-dependent RNA-polymerase (RdRp) and 3C-like proteinase (3CL^{pro}) are two main enzymes that play a key role in the replication of SARS-CoV-2. Zinc (Zn) has strong immunogenic properties and is known to bind to a number of proteins, modulating their activities. Zn also has a history of use in viral infection control. Thus, the present study models potential Zn binding to RdRp and the 3CL^{pro}. Through molecular modeling, the Zn binding sites in the aforementioned two important enzymes of viral replication were found to be conserved between severe acute respiratory syndrome (SARS)-coronavirus (CoV) and SARS-CoV-2. The location of these sites may influence the enzymatic activity of 3CL^{pro} and RdRp in coronavirus disease 2019 (COVID-19). Since Zn has established immune health benefits, is readily available, non-expensive and a safe food supplement, with the comparisons presented here between SARS-CoV and COVID-19, the present study proposes that Zn could help ameliorate the disease process of COVID-19 infection.

Introduction

Zinc (Zn) is an essential metal involved in cell signalling, proliferation, differentiation, oxidative stress, the immune response and numerous other important cellular processes (1-4). The role of Zn in cells is primarily associated with Zn binding as a cofactor in enzymes, or for structural and/or regulatory functions of proteins (5). The immune system is highly dependent on Zn homeostasis for proper and efficient function. Zn is an integral part of the signalling pathways involved in regulating both the innate and adaptive immune responses (3). In individuals with Zn deficiency, these signals are highly perturbed, affecting both T-cell and B-cell development and function, natural killer cell production and monocyte cytotoxicity (3). Due to these perturbations individuals with Zn deficiency are more susceptible to infection (6). In this regard, Zn supplements are heralded to boost the immune system.

The use of Zn against viruses has been studied from the 1970s to present, where Zn was shown to affect viral replication, protein synthesis and processing, membrane fusion and RNA polymerase activity (7-21). A summary of the influence of Zn on several respiratory viruses is provided in Table I.

Clinical studies have linked Zn supplementation with less severe and reduced duration of symptoms along with lower recurrent infections for viral infections (6-7,22). Although there is an observed benefit of Zn in antiviral therapy, this is largely dependent on the type of infection as well as the concentration, formulation and subsequent redox species of Zn used (7). For example, the use of Zn to treat the common cold often caused by rhinoviruses has been extensively reviewed with large variability in treatment effectiveness (7,23-27). While there is evidence of the role of Zn in inhibiting other respiratory viruses such as severe acute respiratory syndrome (SARS)-coronavirus (CoV), the efficacy of Zn in clinical trials against these has not been sufficiently studied with good rigour (7,11).

With the emergence of coronavirus disease 2019 (COVID-19), several studies have explored the therapeutic potential of compounds previously used against similar coronaviruses, such as SARS-CoV and Middle East respiratory syndrome (MERS)-CoV (28,29). Two essential proteins in coronaviruses include: i) RNA-dependent RNA-polymerase (RdRp), which is necessary for proper viral replication, a core enzyme of the viruses' multiprotein replication and transcription complex (30) and ii) 3C-like proteinase (3CL^{pro}) or main protease, a cysteine protease that has two domains each containing β-barrel chymotrypsin-like folds (31). The active site of 3CL^{pro} is located in the cleft between the two domains and is characterized by a catalytic Cys-His dyad, which is necessary for polyprotein processing and essential for viral replication (30,31). For this reason, compounds with the ability to inhibit these proteins are often used as antivirals (32,33).

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Key words: coronavirus disease 2019, severe acute respiratory syndrome-coronavirus-2, coronavirus, zinc, RNA-dependent RNA-polymerase, 3C-like proteinase, enzyme inhibition, nutrition supplements, treatment, prevention

Zn is often delivered as a complex with N-ethyl-N-phenyl dithiocarbamic acid zinc (EPDTC) or toluene-3,4-dithiolato zinc (TDT) (13). These Zn ionophores also contribute to protein binding and inhibit these enzymes (11,12). Zn-ligating compounds are proposed to aid in coordinating Zn in the catalytic site of 3CL^{pro}, thus inhibiting proteinase activity (12,13). Alternatively, Zn ionophores are only thought to aid Zn cell entry where Zn^{2+} ions then act alone to inhibit RdRp, though how this inhibition occurs has not been fully elucidated (11,14).

The presents study performed bioinformatics analysis and modelled Zn binding sites onto RdRp and 3CL^{pro} and proposed the hypothesis that Zn would modulate COVID-19 replication and ameliorate the infection and severity of symptoms.

Materials and methods

RdRp sequences and databases, multiple sequence alignment and phylogenetic tree. The nucleotide sequence of RdRp for COVID-19 (GenBank accession no. MT042778.1), SARS RdRp (GenBank accession no. AY340092.1), influenza A PB1 (GenBank accession no. AJ620348.2), hepatitis C virus (HCV) NS5B (GenBank accession no. AJ608785.1), calcivirus RdRp (GenBank accession no. Y13703.1) and T7 Phage RdRp (GenBank accession no. M3830s28.1) was retrieved in FASTA format from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov).

The amino acid sequence for COVID-19 nsp 12 (GenBank accession no. YP_009725307.1), SARS rep (UniProtKB accession no. R1AB_CVHSA), influenza A PB1 (GenBank accession no. AAK18013.1) and T7 Bacteriophage (T7 Phage) PHA (PDB accession no. 4RNP_C) was obtained from the following databases: NCBI (https://www.ncbi.nlm.nih.gov/protein/), UniProt (https://www.uniprot.org/), Protein Data Bank In Europe (https://www.ebi.ac.uk/pdbe/) and Worldwide Protein Data Bank (http://www.wwpdb.org/). For all DNA and protein phylogenetic trees and multiple sequence alignments, ClustalW and ClustalX were used (http://www.clustal.org/).

3CL^{pro} sequences and databases, multiple sequence alignment and phylogenetic tree. The nucleotide sequence of COVID-19 orf1ab (GenBank accession no. MT049951.1), SARS 3CL^{pro} (GenBank accession no. AY609081.1), black queen cell virus (BQV) 3CL^{pro} (GenBank accession no. KM232906.1), yellow head virus (YHV) 3CL^{pro} (GenBank accession no. EU977577.1) and avian infectious bronchitis virus 3CL^{pro} (GenBank accession no. Q157446.1) was retrieved in FASTA format from the same databases used for RdRp.

The amino acid sequence of 3CL^{pro} COVID-19 nsp5A_3CLpro and nsp5B_3CLpro (NCBI Reference Sequence accession no. YP_009742612.1), SARS Peptidase_C30 (PDB accession no. 3F9G_A), YHV Peptidase_C62 (GenBank accession no. ABL96309.1), BQV 3C-like protease (GenBank accession no. AIW60925.1) and European brown hare syndrome virus 3CL^{pro} (NCBI Reference Sequence accession no. NP_786901.1) was retrieved in FASTA format from the same databases used for RdRp. For all DNA and protein phylogenetic trees and multiple sequence alignment, ClustalW and ClustalX were used (http://www.clustal.org/).

Structural analysis. The previously determined crystal structures of the RdRp of SARS-CoV (PDB accession no. 6NUR) (34) and COVID-19 (PDB accession no. 6M71) (35) were aligned using PyMOL Molecular Graphics system (version 1.2r3pre; Schrödinger, Inc.). The alignment was performed iteratively five times with a cut-off of 2.0 Å and a resulting root-mean-square deviation (RMSD) value of 0.588 for 7,027 atoms aligned out of a total 8,040 atoms. The crystal structures of the 3CL-protease of SARS-CoV bound to a Zn coordinating compound (TLD902; TDT) (PDB accession no. 2Z94) (13) and SARS-CoV-2 (PDB accession no. 6W63) (36) were also aligned iteratively five times with a cut-off of 2.0 Å and a resulting RMSD value of 0.621 for 1,985 atoms aligned out of a total 2,339 atoms in PyMol. The Zn binding sites were illustrated based on the location of Zn in the crystal structure of these proteins for SARS-CoV.

Results

RdRp and 3CL^{pro} of SARS-CoV-2 multiple sequence alignments and phylogenetic trees. The present analysis revealed a high level of identity (81.5 for DNA and 96.2 for protein alignment) of COVID-19 RdRp with the enzyme from the SARS virus that belongs in the same virus family (Coronaviridae). The score, identity and similarity of RdRp DNA and amino acid sequences are shown in Tables SI and SII. Alignment of the DNA sequences of COVID-19 RdRp (GenBank accession no. MT042778.1) and SARS RdRp (GenBank accession no. AY340092.1) showed an 87.7% aligned score of the two sequences (Fig. 1 and Table SI). Moreover, an amino acid sequence alignment of COVID-19 nsp 12 (GenBank accession no. YP_009725307.1) and SARS rep (UniProtKB accession no. R1AB_CVHSA) showed an aligned score of 96.3% for the two sequences (Fig. 1 and Table SII). The alignment score, identity and similarity of RdRp DNA and amino acid sequences are shown in Tables SI and SII.

The same analysis was performed on the enzyme 3CL^{pro} DNA sequence alignment of COVID-19 3CL^{pro} (NCBI Reference Sequence accession no. YP_009742612.1) and 3CL^{pro} (PDB accession no. 3F9G_A), which showed an aligned score of 82% between the two sequences (Fig. 2 and Table SIII). Moreover, an amino acid sequence alignment of COVID-19 nsp5A_3CLpro and nsp5B_3CLpro (NCBI Reference Sequence accession no. YP_009742612.1) and SARS Peptidase_C30 (PDB accession no. 3F9G_A) were aligned with a score of 95% (Fig. 2 and Table SIV). A phylogenetic tree based on COVID-19 and SARS 3CL^{pro} DNA and amino acid sequences is shown in Fig. 2.

Structural analyses of Zn binding to RdRp and 3CL^{pro} of SARS-CoV-2. Based on bioinformatic similarities, structural analyses were performed to evaluate the structural similarity between the RdRp of SARS-CoV and COVID-19 (Figs. 3 and 4). A structural alignment was performed on previously determined crystal structures for RdRp of SARS-CoV (PDB accession no. 6NUR) (34) and COVID-19 (PDB accession no. 6M71) (35). The alignment produced an RMSD value of 0.588 for 7,027 atoms aligned out of a total 8,040 atoms. The Zn binding sites, based on the crystal structure of the SARS-CoV RdRp, were conserved in the COVID-19 RdRp.

Table 1. The influence of zinc, zinc conjugates and zinc ionophores on respiratory viruses.

Virus family	Strain	Antiviral mechanism	Zinc formulation and effective concentration
Coronaviruses	SARS-CoV	Reduced viral replication (11)	2 μM $ZnOAc_2$ + 2 μM PT
		Inhibited RNA synthesis and RdRp activity and template binding (11)	50 μM to 6 mM $ZnOAc_2$
		Inhibition of $3CL^{pro}$ activity (13)	Zinc conjugated TDT (K_i=1.4 μM), EPDTC (K_i=1.0 μM), JMF1600 (K_i=0.32 μM) and JMF1586 (K_i =0.05 μM)
		Inhibition of $3CL^{pro}$ activity (12)	Zn^{2+} ions (K_i=1.1 μM), 1-hydroxypyridine-2-thione zinc (K_i=0.17 μM)
Picornavriuses	CVB3	Reduced viral replication and disrupt polyprotein processing (14,15)	0.1-10 μM $ZnCl_2$ + 125 μM PDTC or 10 μM PT, 125 μM PDTC or 125 μM HK allowing Zn^{2+} cell influx
	Mengovirus	Reduced viral replication and disrupt polyprotein processing (14,15)	0.1-10 μM $ZnCl_2$ + 125 μM PDTC or 10 μM PT, 125 μM PDTC or 125 μM HK allowing Zn^{2+} cell influx
	HRV	Slight reduction in viral replication (16)	0.1 mM Zn gluconate or Zn lactate
		Inhibition of RdRp activity (17)	$ZnCl_2$ (IC_{50}=0.6 μM for PolyA/T template or 4.0 μM for sshRNA template)
	HRV	Reduced viral replication and disrupt polyprotein processing (14,18)	10 μM PT, 125 μM PDTC or 125 μM HK allowing Zn^{2+} cell influx
Paramyxoviridae	RSV	Reduced viral replication and penetration (19)	0.1-10 mM of Zn acetate, Zn sulfate or Zn lactate
Influenza	Influenza A	Reduced viral-induced DNA fragmentation and caspase-3 activity (20)	0.15 mM $ZnSO_4$
	H1N1	Reduced virus titer post-infection (21)	25-200 μg/ml PEGylated ZnO-NPs 75 μg/ml ZnO-NPs

$3CL^{pro}$, 3-cysteine like proteinase; CVB3, coxsackievirus B3; EPDTC, N-ethyl-N-phenyldithiocarbamic acid zinc; HK, hinokitiol; HRV, human rhinovirus; IC_{50}, half-maximal inhibitory concentration; JMF1586, bis(L-aspartato-N,O) zinc(II) ethanate; JMF1600, (nitrilotriacetato-N,O) zinc(II) acetate; K_i, inhibition constant; PDTC, pyrrolidine dithiocarbamate; PEG, polyethylene glycol; PT, pyrithione; RdRp, RNA-dependent RNA-polymerase; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome-coronavirus; sshRNA, secondary structure-less heteropolymeric RNA; TDT, toluene-3,4-dithiolato zinc; Zn, zinc; ZnO-NP, zinc oxide nanoparticle.

A structural alignment between $3CL^{pro}$ of SARS-CoV (PDB accession no. 2Z94) (13) and COVID-19 (PDB accession no. 6W63) (36) was also performed based on previously determined crystal structures (Fig. 5). An RMSD value of 0.621 was obtained for 1,985 atoms aligned out of a total 2,339 atoms between these proteins. Similar to RdRp, the Zn binding site in the crystal structure of SARS-CoV $3CL^{pro}$ was conserved for COVID-19.

Discussion

The antiviral activity of Zn was reported by several studies and shown to effect viral replication, protein synthesis and processing, membrane fusion and RNA polymerase activity (7-21). A previous study by Kirchdoerfer and Ward (34) indicated that RdRp-targeted drugs for SARS have the potential for COVID-19 treatment, and the present analysis suggested that there is similar potential of Zn-targeting RdRp enzymes from this group of viruses (37). Likewise, a phylogenetic tree based on COVID-19 and SARS RdRp DNA and amino acid sequences also supported in hypothesis. Two Zn binding sites were previously identified in the structure of SARS-CoV RdRp, which the present study has shown to be conserved in the COVID-19 RdRp. These sites were hypothesized by the authors of the structure to be important for proper folding of RdRp based on their location in the protein (34). However, it is possible that binding of Zn may also be allosterically regulatory and lead to catalytic inhibition of RdRp in SARS-CoV (11). More enzymology studies would be required to confirm the importance of these sites for either inhibition or folding by Zn atom binding. Previous structural studies with Zn-coordinating compounds and $3CL^{pro}$ of SARS-CoV revealed that Zn bound to the catalytic dyad present in $3CL^{pro}$ with the help of TDT (38). These residues are also found in the aligned structure of COVID-19 $3CL^{pro}$ at the same position, indicating that Zn would also bind to the COVID-19 enzyme catalytic residues. Both Zn alone and the Zn coordinating compounds were effective inhibitors of $3CL^{pro}$ of SARS-CoV activity with a K_i of 1.1, 1.4 and 1.0 μM for Zn alone, TDT and EPDTC, respectively (12). Therefore, considering the current COVID-19 pandemic and the present data, the present study hypothesized that Zn supplementation would be applicable in clinical practice to modulate symptoms and replication of the virus.

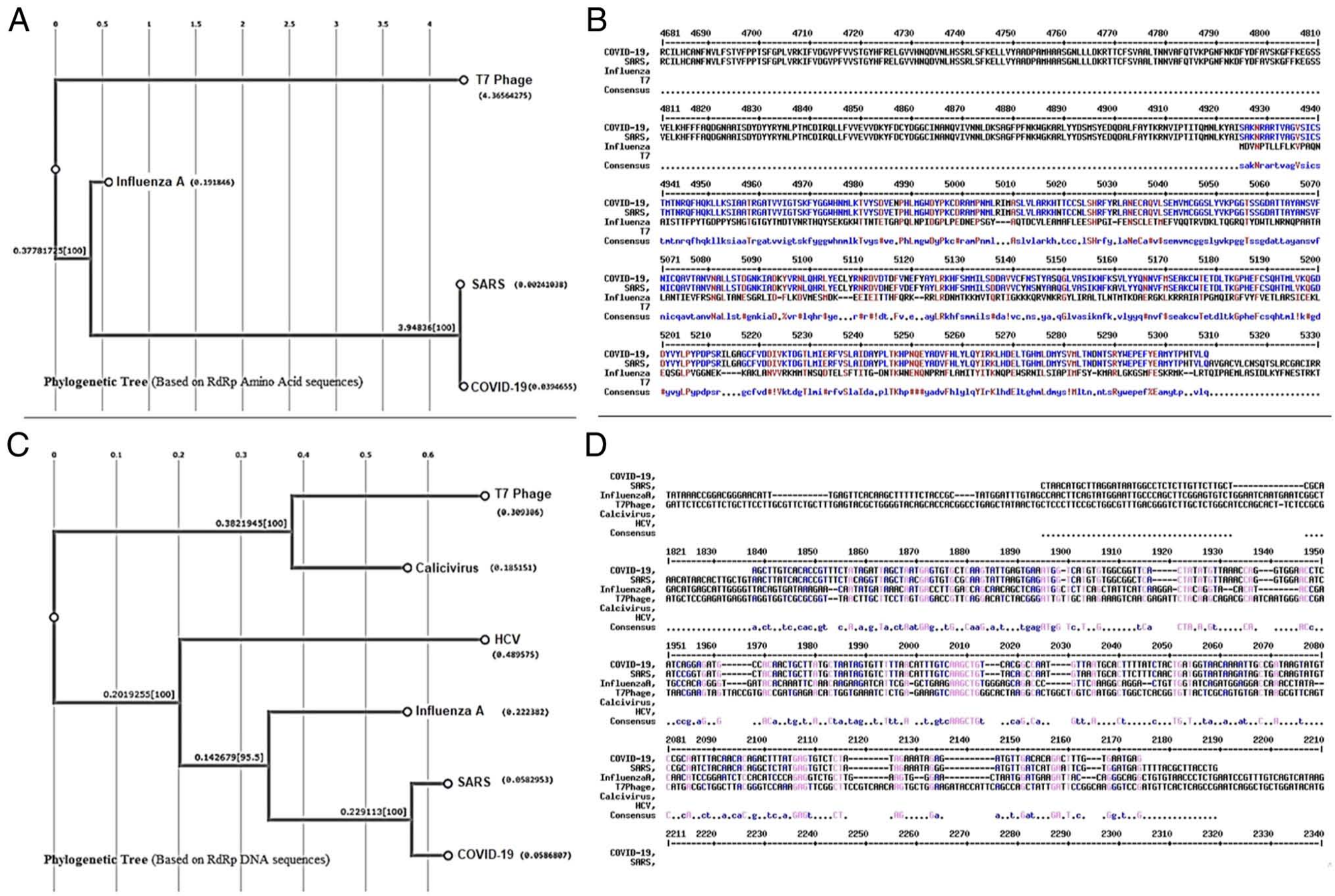

Figure 1. Phylogenetic trees and multiple sequence alignments of COVID-19 RdRp. (A) Phylogenetic tree using ClustalW software and (B) multiple sequence alignment using CLUSTAL 2.1 based on amino acid sequences of COVID-19 nsp 12 (GenBank accession no. YP_009725307.1), SARS rep (UniProtKB accession no. R1AB_CVHSA), influenza A PB1 (GenBank accession no. AAK18013.1) and T7 Bacteriophage (T7 Phage) PHA (PDB accession no. 4RNP_C). (C) Phylogenetic tree and (D) Multiple sequences alignment based on DNA sequences of COVID-19 RdRp (GenBank accession no. MT042778.1), SARS RdRp (GenBank accession no. AY340092.1), influenza A PB1 (GenBank accession no. AJ620348.2) and hepatitis C virus NS5B (GenBank accession no. AJ608785.1), calcivirus RdRp (GenBank accession no. Y13703.1) and T7 Phage RdRp (GenBank accession no. M3830s28.1). RdRp, RNA-dependent RNA polymerase; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome.

With the emergent threat of the COVID-19 virus, several studies have explored the therapeutic potential of compounds previously used against similar coronaviruses (SARS-CoV and MERS-CoV) (28,29). Recent meta-analyses by our research group showed the similarities of COVID-19 with other respiratory viral infections such as SARS, MERS and influenzas (39,40). Clinical studies have linked Zn supplementation with less severe and reduced duration of symptoms along with lower recurrent infections for viral infections (6,7,22).

Several studies have identified lungs as one of the earlier organs to fail due to inflammation in COVID-19 cases (41-44). Lung failure is one of the most important leading causes of severe outcomes, including death, in these cases (41-46). Our recent meta-analysis on 52,251 confirmed cases of COVID-19 indicated an increase to pre-inflammatory factors such as IL-6 present in 52% of cases (39). Therefore, researchers are focusing on anti-inflammatory drugs such as anti-IL-6 for treatment of patients with COVID-19 (42,47-49). Previous studies revealed a key role for Zn in the regulation of inflammation, especially for lungs; Gammoh and Rink (50) reported that Zn is critical in the prevention of host-tissue damage by inflammation, controlling oxidative stress and regulating inflammatory cytokines. Zn is involved in modulating inflammation by decreasing IL-6 and pro-inflammatory responses via reducing NF-κB, the master regulator of pro-inflammatory responses (50). NF-κB can regulate inflammatory responses by targeting genes, such as TNF-α and IL-1β, as well as increasing the expression of A20 and peroxisome proliferator-activated receptors-α genes (50,51). Moreover, a study by Knoell *et al* (52) showed that insufficient Zn can actually enhance lung inflammation.

Additionally, the overuse and abuse of antibiotics is of increasing concern, particularly during treatment of respiratory infections (53-56). Although co-infection of viruses and bacteria can occur, identifying these cases can be challenging (57,58). Lack of appropriate antimicrobial stewardship programs and overprescription and use of antibiotics in viral infections such as the novel COVID-19 can lead to antibiotic side effects and antimicrobial resistance (AMR) (59,60). Both suspected and confirmed cases of COVID-19 have received broad-spectrum antibiotics as there is currently no rapid method that distinguishes between cases which need antibiotic treatment and those that do not (61,62). Although it is lifesaving in some patients, in others this treatment may be excessive and lead to antibiotic side effects such as septic shock, killing normal microbiota and contribute to AMR (62-64).

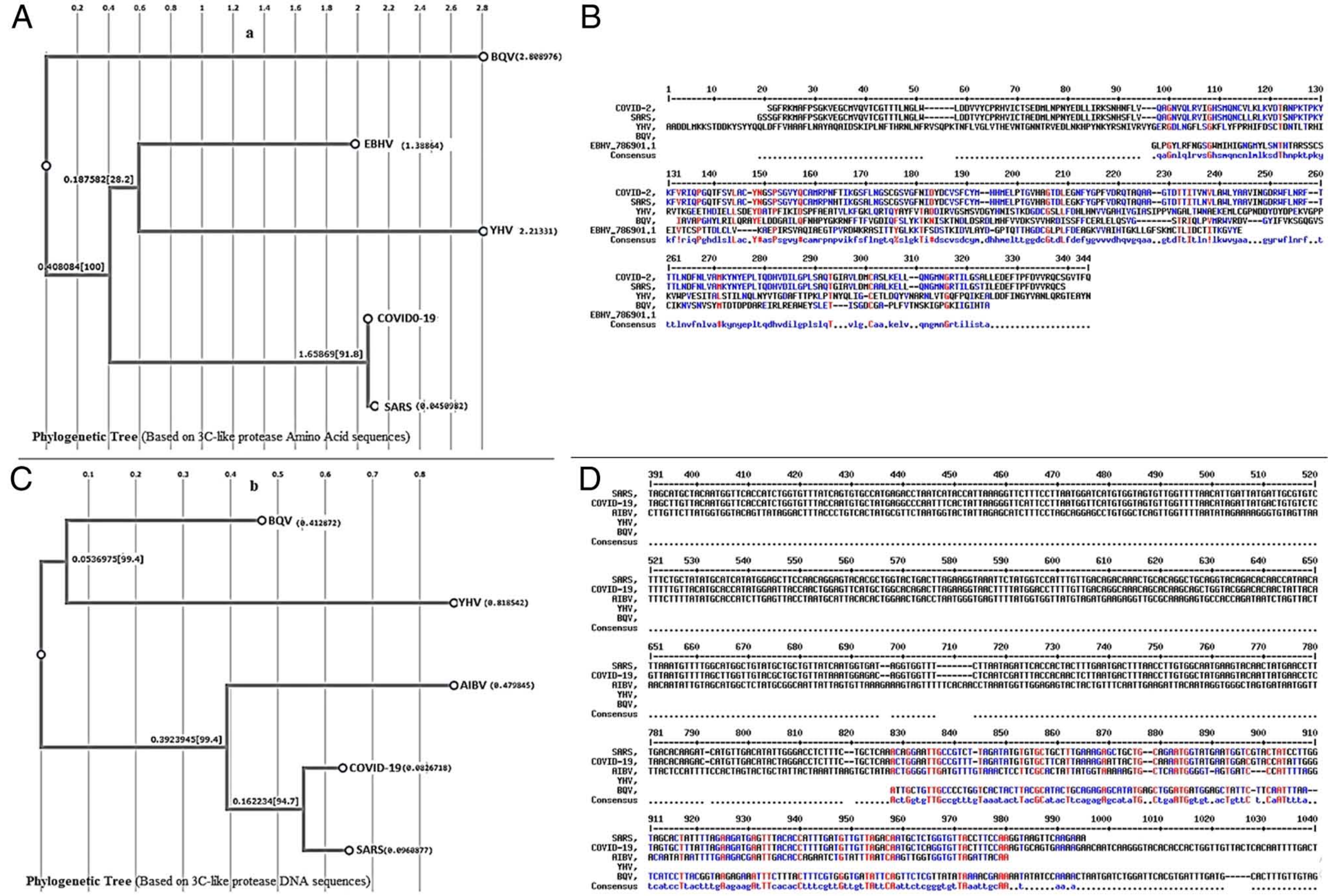

Figure 2. Phylogenetic trees and multiple sequence alignments of COVID-19 3CL^{pro}. (A) Phylogenetic tree using ClustalW software and (B) multiple sequence alignment using CLUSTAL 2.1 based on amino acid sequences of COVID-19 nsp5A_3CLpro and nsp5B_3CLpro (NCBI Reference Sequence accession no. YP_009742612.1), SARS peptidase_C30 (PDB accession no. 3F9G_A), YHV peptidase_C62 (GenBank accession no. ABL96309.1), BQV 3C-like protease (GenBank accession no. AIW60925.1) and European brown hare syndrome virus 3CL^{pro} (NCBI Reference Sequence accession no. NP_786901.1). (C) Phylogenetic tree and (D) multiple sequence alignment based on DNA sequences of COVID-19 orf1ab (GenBank accession no. MT049951.1), SARS 3CL^{pro} (GenBank accession no. AY609081.1), BQV 3CL^{pro} (GenBank accession no. KM232906.1), YHV 3CL^{pro} (GenBank accession no. EU977577.1) and avian infectious bronchitis virus 3CL^{pro} (GenBank accession no. Q157446.1). YHV, yellow head virus; BQV, black queen cell virus; 3CL^{pro}; 3C-like protease; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome.

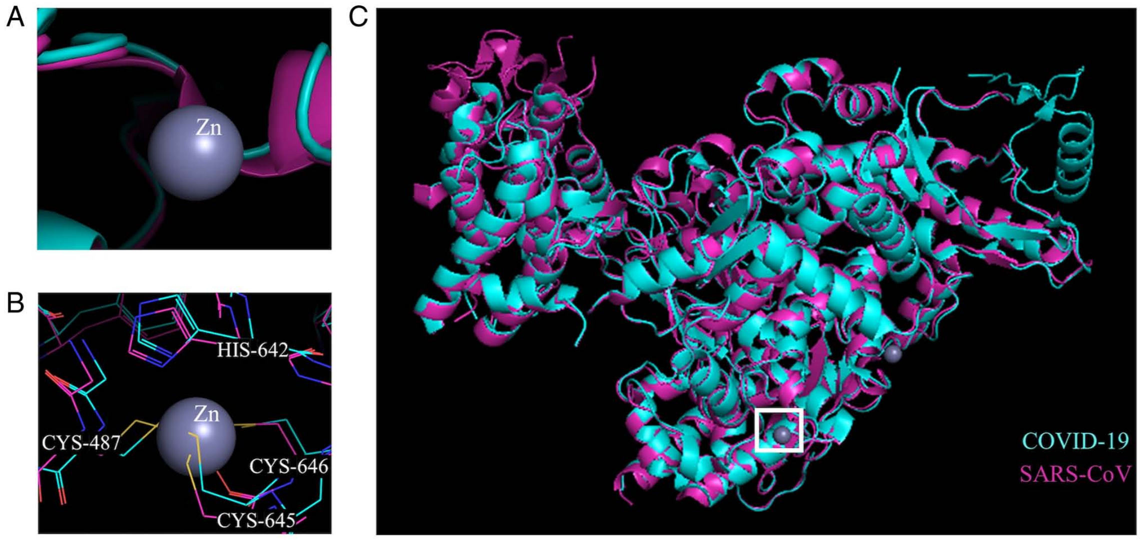

Figure 3. Structural alignment between SARS-CoV (pink) and COVID-19 (cyan) of the RdRp. (A and B) The first zinc binding site and (C) overall structure. The white box indicates the area where zinc binds on the overall structure. The structures were aligned on PyMol using previously determined crystal structures for RdRp in SARS-CoV (PDB accession no. 6NUR) and COVID-19 (PDB accession no. 6M71). The alignment was performed iteratively five times with a cut-off of 2.0 Å and a resulting root-mean-square deviation value of 0.588 for 7,027 atoms aligned out of a total 8,040 atoms. RdRp, RNA-dependent RNA polymerase; SARS, severe acute respiratory syndrome; CoV, coronavirus; HIS, histidine; CYS, cysteine.

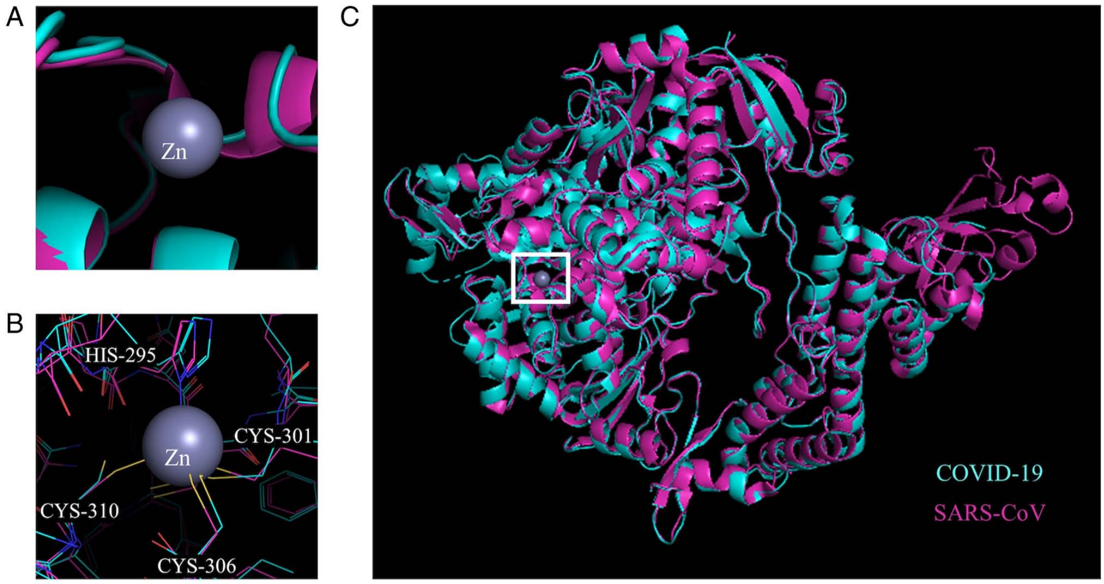

Figure 4. Structural alignment between SARS-CoV (pink) and COVID-19 (cyan) of the RdRp. (A and B) The second zinc binding site and (C) overall structural alignment. The white box indicates the area where zinc binds based on the overall structure. The structures were aligned on PyMol using previously determined crystal structures for RdRp in SARS-CoV (PDB accession no. 6NUR) and COVID-19 (PDB accession no. 6M71). The alignment was performed iteratively five times with a cut-off of 2.0 Å and a resulting root-mean-square deviation value of 0.588 for 7,027 atoms aligned out of a total 8,040 atoms. RdRp, RNA-dependent RNA polymerase; SARS, severe acute respiratory syndrome; CoV, coronavirus; HIS, histidine; CYS, cysteine.

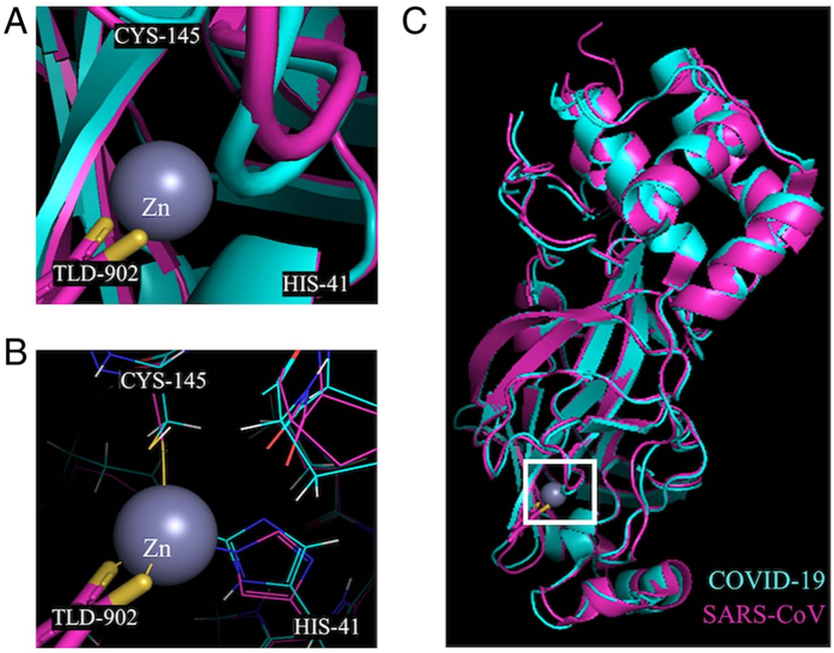

Figure 5. Structural alignment between SARS-CoV (pink) and COVID-19 (cyan) of the 3CL^{pro} bound to a zinc coordinating compound (TLD-902; TDT). Subtitle: The alignment and structures were modelled with PyMol using previously determined crystal structures for the 3CL^{pro} of SARS-CoV bound to TDT (PDB accession no. 2Z94) and 3CL^{pro} of COVID-19 (PDB accession no. 6W63). The alignment was performed iteratively five times with a cut-off of 2.0 Å and a resulting root-mean-square value of 0.621 for 1,985 atoms aligned out of a total 2,339 atoms. (A and B) Zinc is shown here to specifically target the catalytic dyad C145 and H41 for inhibition, which are unaltered between SARS-CoV and COVID-19. (C) The overall structural alignment is also displayed with a white box indicating the location of the zinc binding site in relation to the full protein. TDT, toluene-3,4-dithiolato zinc; 3C-like proteinase, 3CL^{pro}; HIS, histidine; CYS, cysteine.

Our research group has been investigating metal-based antimicrobials in response to the AMR era (65-69). A number of different metal elements being reintroduced into regular infection control applications have been observed (68). Studies have now established the antibacterial potency of Zn, as either a metal salt or metal oxide nanoparticle, against common pathogenic strains (70) and clinical isolates (71-73). Therefore, the use of Zn can be considered for use in both viral and bacterial disease states.

Zn is recommended by the National Institutes of Health (NIH) for inducing the immune system and preventing viral infections; however, the amount of Zn people requires each day depends on age (74). While Zn supplementation is necessary to correct any deficiency, an overabundance of Zn can also lead to a variety of physiological dysfunctions. Excess Zn can lead to copper deficiency, alter lymphocyte response and inhibit T-cell function (75). Therefore, the use of Zn for therapeutic purposes should still be monitored based on food intake and use of supplements. Although Zn is relatively non-toxic to humans with an median lethal dose of 3 g/kg weight, extreme excess Zn (>100-300 mg/day) should be avoided; the NIH considers 40 mg of zinc a day for adults and 4 mg of zinc a day for infants under 6 months to be the upper limit dose (75).

The aforementioned points support the potential use of Zn in the clinical treatment of COVID-19 patients. However, the main obstacle for the current study is limited supportive clinical data for prevention and treatment potency of Zn in patients with COVID-19.

Most people obtain their daily required Zn through a healthy diet. However, the dietary oral intake supplements of 15-25 mg Zn tablets per day is recommended to help aid immune response in the short term (4). Currently, there is no consensus that Zn is helpful for the prevention and treatment of COVID-19 infection. However, the present bioinformatics and molecular modeling analysis supported the hypothesis that Zn would bind and regulate the enzymatic activities of $3CL^{pro}$ and RdRp of SARS-CoV-2 and thus inhibit viral replication. Further studies would be necessary to identify the exact mechanism by which this could occur in the COVID-19 viral-cell cycle processes. More studies are necessary to understand the molecular mechanisms, effective concentration and delivery formulations. Zn may be considered a candidate for the prevention and treatment of COVID-19 infection.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Sciences Engineering Research Council of Canada to RJT.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AP and RJT conceived and designed the study; NKM and AP performed comprehensive research; AP and NKM analyzed the data; AP, NKM and RJT wrote and revised the paper; AP, NKM and RJT participated in data analysis and manuscript editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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