SPC

Advanced Journal of Chemistry-Section A

Journal homepage: www.ajchem-a.com

Short Communication

Microbial Iron Chelators: A Possible Adjuncts for Therapeutic Treatment of SARS-CoV-2 like Viruses

Swapnil Mahajan[1] *, Muntjeeb Syed[1], Shridhar Chougule[2]

[1]*Division of Biochemistry, Department of Chemistry, Savitribai Phule Pune University, Pune-411007, Maharashtra, India*

[2]*Department of Biotechnology, Savitribai Phule Pune University, Pune-411007, Maharashtra, India*

ARTICLE INFO

Article history

Submitted: 13 October 2022
Revised: 05 December 2022
Accepted: 07 December 2022
Available online: 08 December 2022
Manuscript ID: AJCA-2210-1335
Checked for Plagiarism: Yes

DOI: 10.22034/AJCA.2023.365582.1335

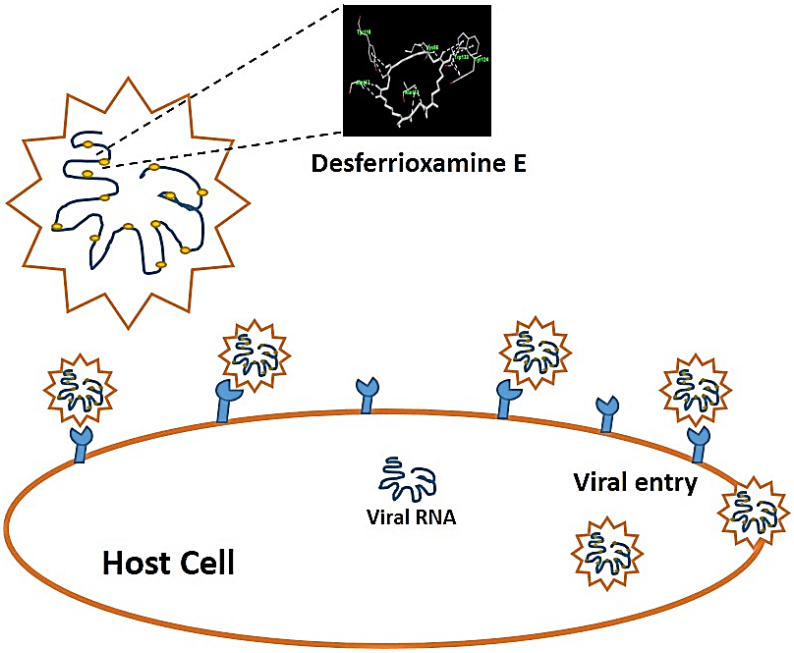
KEYWORDS

Iron chelator
Siderophore
Desferrioxamine E
SARS-CoV-2
Molecular docking

ABSTRACT

There is a need for targeted, effective antiviral therapeutic treatment for the global threat of COVID-19, like viral pandemics. Our efforts in this direction present the in-silico testing of a hypothesis through molecular docking. We have demonstrated the possibility of a microbial siderophore desferrioxamine-E produced by *Pseudomonas stutzeri* SGM-1 for effective drug targeting and drug development against SARS-CoV-2, like viruses. Iron homeostasis and COVID-19 have a close relationship. An iron chelator desferrioxamine-E binding with the SARS-CoV-2 virus can inhibit the viral RNA binding and packaging into the new virions inside the host cell. The well-known efficacy of iron chelation and RNA binding domain of SARS-CoV-2 nucleocapsid interaction of desferrioxamine-E studied through molecular docking has promising potential for exploring microbial iron chelators as adjuncts for in-silico clinical trials and randomized clinical trials.

GRAPHICAL ABSTRACT



* Corresponding author: Mahajan, Swapnil
✉ E-mail: swapnilmahajan87@gmail.com

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a causative agent for COVID-19 disease, which was declared a global pandemic officially by WHO (World Health Organization) on Mar 11, 2020 [1]. From the onset of the third wave, still in 2022, there is a threat of continuous rise with reports of new outbreaks of positive COVID-19 cases associated with the increased death toll. Despite vaccination on a larger scale, in most countries, there is a need to prevent and eradicate different coronavirus variants. Iron is essential for the growth and living of nearly all the life forms on the earth. The redox potential of iron helps fix or harvest energy through different metabolic processes among different life forms; autotrophic and heterotrophic [2,3]. Many catalytic biotransformation processes involve specialized enzymes with iron as their cofactor [4]. In mammalian cells, iron is majorly accumulated as tightly bound to proteins like hemoglobin and ferritin and transported via transferrin and lactoferrin [5]. New targeted therapeutic drugs would be the best treatment for such viral pandemics [6].

The genome of the SARS-CoV-2 virus consists of a single-stranded RNA like earlier MERS–CoV and SARS-CoV [7]. In December 2019, this β-coronavirus (nCoV), was first identified and reported from the respiratory tract of a patient with pneumonia in Wuhan, Hubei, China. This SARS-CoV-2 virus had unique and complete components for human immune invasion, ultimately leading to infectivity and fatality of its hosts. A typical SARS-CoV-2 virion structurally has four main structural proteins viz., S-protein (Spike glycoprotein), E-protein (small envelope glycoprotein), M-protein (Membrane glycoprotein), and N-protein (Nucleocapsid protein) [7]. Among these proteins, the N-protein for nucleocapsid is an essential protein for the viral structural assembly, as it binds to the RNA and packaging into the nucleocapsid's long helical structures, called the ribonucleoprotein complex (RNP) [8,9]. This protein plays a vital role in viral transcription, replication, and viral infection-associated cellular response of the host cells [10,11]. The N-protein domain architecture is composed of two highly conserved shared domains, the N-terminal RNA-binding domain (NTD) and the C-terminal dimerization domain (CTD) [12,13].

The therapeutic strategies against SARS-CoV-2-like viruses involve the targets of viral entry into the host, RNA transcription, replication, and protein processing [14]. Antiviral drugs like Remdesivir, earlier developed for the Ebola virus [15,16], inhibit the RNA-dependent RNA polymerase enzyme of the SARS-CoV-2 virus [17]. The trace but essential element iron is significant as it is involved in DNA/RNA synthesis, repair, and other different physiological processes [18]. Like human host cells, the infectious SARS-CoV-2 also needs iron to complete its replication process, which involves various iron-containing enzymes. Inside the host organism, the SARS-CoV-2 virus and the host cells actively compete for iron availability for the above reasons. Recently, patients with SARS-CoV-2 infection have reported a high ferritin level [19]. However, it is unclear that this possibility is because of novel coronavirus hepcidin-like action, which can directly increase ferritin levels regardless of the inflammatory effect [20]. Thus, iron chelation can be an essential strategy in treating viral infections [21]. The iron chelator drug's action involves inhibiting viral replication and modulating host cell cellular iron homeostasis [22].

Experimental

In light of the facts mentioned above, an attempt has been made to study an iron chelator desferrioxamine-E of an indigenous salt-tolerant *Pseudomonas stutzeri* strain SGM-1 [23] isolated from saline soil habitat [24]. The iron chelator

desferrioxamine-E is pharmaceutically known as nocardamine, which we have tested here for targeting the N-terminal RNA binding domain of the SARS-CoV-2 viral nucleocapsid protein. The structure of the N-terminal RNA binding domain of the SARS-CoV-2 viral nucleocapsid protein (PDB: 6M3M, 2.70 Å resolution, 2020) was obtained from the protein data bank (PDB). The chemical structure of the iron chelator desferrioxamine-E, also called nocardamine was downloaded from PubChem (CID 167865). The ligand-protein interaction was studied by docking with AutoDock 1.5.6, Discovery Studio Visualizer (DSV) 2.1, and Cygwin64. The internal conformation in AutoDock was searched with the help of the Genetic Algorithm (GA) and Lamarckian Genetic Algorithm [25], producing an ensemble of conformations. The binding energy is calculated by AutoDock 1.5.6 software whereas, the inhibition constant (K*i*) was obtained from the binding energy (ΔG) using the formula: $Ki = \exp(\Delta G/RT)$, where R is the universal gas constant (1.985×10^{-3} kcal mol^{-1} K^{-1}). T is the temperature (25 °C) [26]. The lowest binding energy conformer was searched out of 10 different conformers, and for each docking simulation, the best scoring pose was judged by Cygwin64. Chosen ligand-protein complex was further analyzed and visualized using DSV software.

Results and discussion

The best docking result of desferrioxamine-E with the N-terminal RNA binding domain of SARS-CoV-2 nucleocapsid protein is shown in Figure 1. The best binding energy and inhibition constant of desferrioxamine-E were found, - 6.92 $kcal.mol^{-1}$ and 8.52 μM, respectively.

Desferrioxamine-E molecule showed hydrogen bonding interaction with Trp133 and hydrophobic interactions with Tyr124, Ala153, Ala157, Lys66, and Tyr110. The microenvironment of COVID-19 protein changes with desferrioxamine-E because there are several interacting tryptophan, tyrosine, alanine, and lysine residues around the binding pocket of the desferrioxamine-E molecule. This specific interaction leads to conformational changes in the SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain. Apart from depriving iron to the virus, the interaction with amino acid residues of the viral N-terminal RNA binding domain by desferrioxamine-E could inhibit RNA binding and its packaging into new virions.

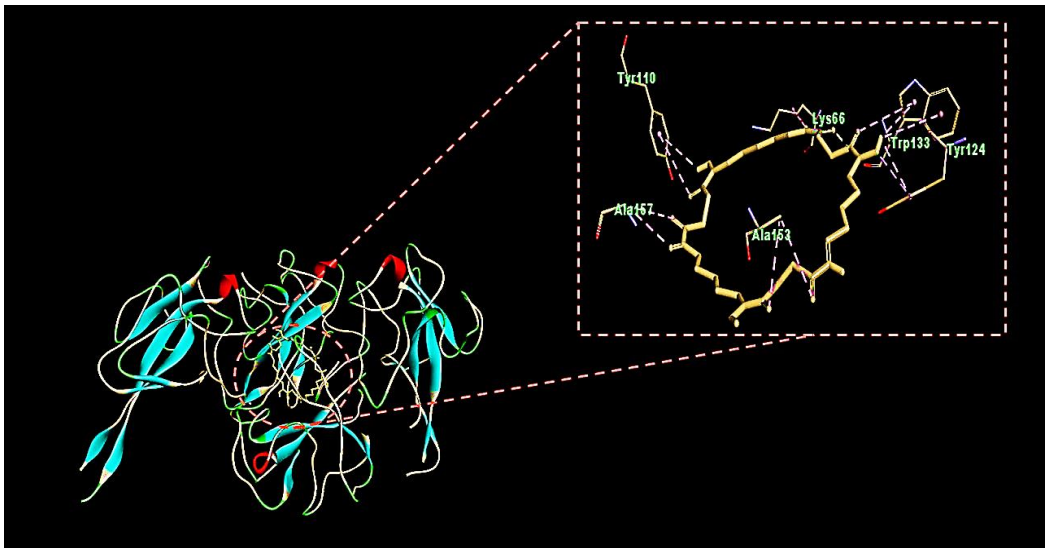


Figure 1. Desferrioxamine-E interaction with SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain

Research efforts are focused on spike protein and viral proteases, while the N-protein of SARS-CoV-2 could be an excellent drug target. The N-protein has a pivotal role in the virus life cycle, like RNA binding, dimerization, and RNA packaging in new nucleocapsids of coronaviruses inside the infected host cells. The desferrioxamine-E has already been reported for its iron chelation and antiviral and immunomodulatory effect in vitro and in vivo [22,27]. Iron homeostasis and COVID-19 have a close relationship, and the cytokine storm associated with the infection can be mitigated with the effective use of iron chelators [28]. Desferrioxamine-E is the high-affinity iron chelator that can deprive available iron in the viral microcosm and bind to the SARS-CoV-2 nucleocapsid RNA binding domain [22,29]. Although oral administration of desferrioxamine drugs is impossible because of poor absorption capacity and related pharmacokinetics, it is used directly intramuscularly or with continuous intravenous infusions [30]. Desferrioxamine-E binding can inhibit the viral RNA binding and packaging into the new virions inside the host cell. This dual therapeutic role of this iron chelator can be further explored as an adjunct for effective drug targeting and drug development for the treatment of SARS-CoV-2 [29].

Conclusions

Based on the docking study and limited data, a hypothesis was proposed for using iron chelators like desferrioxamine-E as an adjunct for effective drug targeting and drug development for the treatment of SARS-CoV-2-like viruses. The docking result of desferrioxamine-E with SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain resulted in the best binding energy and inhibition constant of desferrioxamine-E as - 6.92 kcal mol^{-1} and 8.52 µM, respectively. The interaction of desferrioxamine-E molecule was found with Trp133 with hydrogen bonding and with hydrophobic interactions for Tyr124, Ala153, Ala157, Lys66, and Tyr110. Although our hypothesis needs to be explored through randomized clinical trials (RCTs) for its usability as an adjunct, this idea of using iron chelator as an adjunct could advance for effective drug targeting of the existing iron chelator drugs for such viral diseases.

Acknowledgment

The author acknowledges the Department of Chemistry, Savitribai Phule Pune University, Pune-07.

Disclosure statement

The authors reported no potential conflict of interest.

ORCID

Swapnil Mahajan: 0000-0001-9518-6239

Muntjeeb Syed: 0000-0001-9116-4374

Shridhar Chougule: 0000-0002-9020-647X

References

[1] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S. Leung, E.H. Lau, J.Y. Wong, X. Xing, *N. Engl. J. Med*. **2020**, *382*, 1199–1207. [CrossRef], [Google Scholar], [Publisher]

[2] B.T. Paul, D.H. Manz, F.M. Torti, S.V. Torti, *Expert Rev. Hematol*., **2017**, *10*, 65–79. [CrossRef], [Google Scholar], [Publisher]

[3] A.F. López-Millán, D. Duy, K.Philippar, *Front. Plant Sci*., **2016**, *7*, 178. [CrossRef], [Google Scholar], [Publisher]

[4] R. Cammack, J.M. Wrigglesworth, H. Baum, *Iron-Dependent Enzymes in Mammalian Systems*, CRC Press, **1990**, pp. 17–39. [Google Scholar]

[5] J. Wang, K. Pantopoulos, *Biochem. J.*, **2011**, *434*, 365–381. [CrossRef], [Google Scholar], [Publisher]

[6] R.A. Dwek, J.I. Bell, M. Feldmann, N. Zitzmann, *Lancet*, **2022**, *399*, 1381–1382. [CrossRef], [Google Scholar], [Publisher]

[7] A.A.T. Naqvi, K. Fatima, T. Mohammad, U. Fatima, I.K. Singh, A. Singh, S.M. Atif, G. Hariprasad, G.M. Hasan, M.I. Hassan, *Biochim. Biophys. Acta Mol. Basis Dis.*, **2020**, *1866*, 165878. [CrossRef], [Google Scholar], [Publisher]

[8] D. Schoeman, B.C. Fielding, *Virol. J.,* **2019**, *16*, 69. [CrossRef], [Google Scholar], [Publisher]

[9] W. Tai, L. He, X. Zhang, J. Pu, D. Voronin, S. Jiang, Y. Zhou, L. Du, *Cell. Mol. Immunol*., **2020**, *17*, 613–620. [CrossRef], [Google Scholar], [Publisher]

[10] P.S. Masters, L.S. Sturman, *Background paper. Functions of the coronavirus nucleocapsid protein*., Springer: Boston, MA. **1990**, pp. 235–238. [CrossRef], [Google Scholar], [Publisher]

[11] R. McBride, M. van Zyl, B. Fielding, *Viruses*, **2014**, *6*, 2991–3018. [CrossRef], [Google Scholar], [Publisher]

[12] S. Kang, M. Yang, Z. Hong, L. Zhang, Z. Huang, X. Chen, S. He, Z. Zhou, Z. Zhou, Q. Chen, Y. Yan, *Acta Pharm. Sin. B.*, **2020**, *10*, 1228–1238. [CrossRef], [Google Scholar], [Publisher]

[13] S Q. Ye, A.M.V. West, S. Silletti, K.D. Corbett, *Protein Sci.*, **2020**, *29*, 1890–1901. [CrossRef], [Google Scholar], [Publisher]

[14] Y.W. Zhou, Y. Xie, L.S. Tang, D. Pu, Y.J. Zhu, J.Y. Liu, X.L. Ma, *Sig. Transduct. Target. Ther.,* **2021**, *6*, 317. [CrossRef], [Google Scholar], [Publisher]

[15] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H.C. Hui, N. Larson, *Nature*, **2016**, *531*, 381–385. [CrossRef], [Google Scholar], [Publisher]

[16] D. Siegel, H.C. Hui, E. Doerffler, M.O. Clarke, K. Chun, L. Zhang, S. Neville, E. Carra, W. Lew, B. Ross, Q. Wang, *J. Med. Chem*., **2017**, *60*, 1648–1661. [CrossRef], [Google Scholar], [Publisher]

[17] C.J. Gordon, E.P. Tchesnokov, J.Y. Feng, D.P. Porter, M. Gotte, *J. Biol. Chem*., **2020**, *295*, 4773–4779. [CrossRef], [Google Scholar], [Publisher]

[18] Y. Khodour, L.S. Kaguni, J. Stiban, *Enzymes*, **2019,** *45,* 225-256. [CrossRef], [Google Scholar], [Publisher]

[19] M. Edeas, J. Saleh, C. Peyssonnaux, *Int. J. Infect. Dis*., **2020**, *97*, 303–305. [CrossRef], [Google Scholar], [Publisher]

[20] A. Cavezzi, E. Troiani, S. Corrao, *Clin. Pract.*, **2020**, *10*, 1271. [CrossRef], [Google Scholar], [Publisher]

[21] W. Liu, S. Zhang, S. Nekhai, S. Liu, *Curr. Clin. Microbiol. Rep*., **2020**, *7*, 13–19. [CrossRef], [Google Scholar], [Publisher]

[22] M. Dalamaga, I. Karampela, C.S. Mantzoros, *Metabolism*, **2020**, *108*, 154260. [CrossRef], [Google Scholar], [Publisher]

[23] S.G. Mahajan, V.S. Nandre, K.M. Kodam, M.V. Kulkarni, *Biocatal. Agric. Biotechnol*., **2021**, *35*, 102057. [CrossRef], [Google Scholar], [Publisher]

[24] S.G. Mahajan, V.S. Nandre, R.C. Salunkhe, Y.S. Shouche, M.V. Kulkarni, *Biocatal. Agric. Biotechnol.*, **2020**, *27*, 101652. [CrossRef], [Google Scholar], [Publisher]

[25] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, *J. Comput. Chem.*, **1998**, *19*, 1639–1662. [CrossRef], [Google Scholar], [Publisher]

[26] C.L.D. Ortiz, G.C. Completo, R.C. Nacario, R.B. Nellas, *Sci. Rep*., **2019**, *9*, 17096. [CrossRef], [Google Scholar], [Publisher]

[27] A. Williams, D. Meyer, *Curr. Pharm. Des*., **2009**, *15*, 1261–1268. [CrossRef], [Google Scholar], [Publisher]

[28] C. Perricone, E. Bartoloni, R. Bursi, G. Cafaro, G.M. Guidelli, Y. Shoenfeld, R. Gerli, *Immunol. Res.*, **2020**, *68*, 213–224. [CrossRef], [Google Scholar], [Publisher]

[29] P.P. Naseef, M. Elayadeth-Meethal, K.T. Mohammed Salim, A. Anjana, C. Muhas, K. Abdul Vajid, M.S. Kuruniyan, *Saudi J. Biol. Sci.*, **2022**, *29*, 1947–1956. [CrossRef], [Google Scholar], [Publisher]

[30] G. Jones, S.K. Goswami, H. Kang, H.S. Choi, J. Kim, *Nanomedicine*, **2020**, *15*, 1341–1356. [CrossRef], [Google Scholar], [Publisher]

HOW TO CITE THIS ARTICLE

Swapnil Mahajan*, Muntjeeb Syed, Shridhar Chougule. Microbial Iron Chelators: A Possible Adjuncts for Therapeutic Treatment of SARS-CoV-2 like Viruses. *Adv. J. Chem. A*, **2023**, 6(1), 65-70.

DOI: 10.22034/AJCA.2023.365582.1335
URL: http://www.ajchem-a.com/article_162482.html