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SHORT COMMUNICATION

Binding ability of arginine, citrulline, *N*-acetyl citrulline and thiocitrulline with SARS COV-2 main protease using molecular docking studies

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Abstract
In this article, the binding abilities of arginine, citrulline, *N*-acetyl citrulline and thiocitrulline on the active sites of SARS-COV-2 protease have been investigated using in-silico studies. All the above ligands bind selectively and preferentially to Cys-145 active site and also to other amino acids surrounding to it in the main protease. Of which arginine forms less number of weaker bonds compared to the other ligands, it by itself is a precursor for the formation of citrulline analogues with in the cell. Major advantage of using the above ligands is that in addition to its preferential binding, they have the ability to increase the immunity by assisting NO generation. Our results show that *N*-acetyl citrulline, citrulline, thiocitrulline and arginine may be used as a supplement during the treatment of SARS-COV-2.

Keywords SARS-COV-2 main protease · Citrulline analogues · Nitric oxide · Immunity

1 Introduction

As per the WHO situation status report dated 24th April 2020, 26,26,321 persons have been infected by SARS-COVID-2, of which 1,81,938 are dead (WHO situation reports 95). The spreading of this pandemic SARS-COVID-2 continues and seems to not cease very soon. One of the major hindrances is in its higher rate of spreading and till date, there are no effective drugs for treatment of infected ones (Lai et al. 2020). Scientists and researchers across the world are intensively engaged in the development of vaccine and development of drugs to curb it (Le et al. 2020; Eynde 2020). Development of new vaccine and also new drug molecules cannot meet the immediate requirement as they have to go through clinical trials and its efficacy as well the protocol for its administration has to be established. An alternative option is to screen the drugs which have already been approved by FDA and used for the treatment of various types of other viruses and test them on SARS COVID-2 virus (Dai et al. 2020; Ul Qamar et al. 2020; Univ. of British Columbia Group 2020; Kadioglu et al. 2020; Tu et al. 2020). Computational chemists and biologists by adopting the combinatorial procedures have verified majority of the available drugs/compounds and the best of them have been examined for their binding ability to main protease of SARS COV-2 (Wang 2020). Recently, hydroxychloroquine in combination with azithromycin was considered to be a potent drug and has been used to treat the infected patients (Rolain et al. 2007; Gautret et al. 2020; Liu and Li 2020). If the patients are already suffering from health issues, then this drug may have other secondary effect as well (Molina et al. 2020). Also remdesivir have also been tested for the COVID 19 infected patients and has been found to be not very effective (Wang 2020). Antiviral drug niclosamide has been proposed to be a potential drug for the treatment of SARS-COV-2 (Xu et al. 2020).

Majority of patients die due to lack of oxygen supply to the system as spike protein of SARS-COV-2 binds to ACE2 enzyme thereby affecting alovelar cells of the lungs (Jin et al. 2020). It is also found that SARS-COV-2 is also affecting the neurons/haemoglobin and other organs as well (Basilio 2020a; b). Recently, there was a report on in-silico studies on the use of *N*-acetyl cysteine/zinc-acetyl cysteine to treat infected lungs (Guthappa 2020). Instead of targeting only lungs, it will be highly recommended, if we could

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choose the molecules/ligands which has both the binding affinity to m-protease as well boost the overall immune system. Nitric oxide is known to have antibacterial and antiviral property (Jones et al. 2010). NO is produced by the tissues in the body and controls cardiovascular, immune and nervous systems (Akaike and Maeda 2020). Gaseous nitric oxide is also released in the respiratory tract of humans during the exhaling process (Lorenzo Berr et al. 2020). Recently, there was a report on the use of nitric oxide for the treatment of SARS-COV-2 (Eby 2006). Major disadvantage is that instead of using directly nitric oxide, it will be safer to use the molecules/compounds which could generate nitric oxide in-vivo thereby enhancing its permeability to all the tissues in the body and bind to m-protease. L-Arginine acts as a precursor to nitric oxide generation in the body (Rajapakse and Mattson 2009). We could also find citrulline and its analogues, as citrulline is a non-essential amino acid produced from arginine by a peptidyl arginine deaminase enzyme. L-Citrulline can also be reversibly converted to L-arginine by argininosuccinate synthase (Guayao and Brosnan 1992). Citrulline residues have been found in myelin basic protein (MBP) and some of the histone proteins (Drug Bank, Canada 2020). Hence, L-citrulline has been tested as a nutraceutical and found to have least side effects. NO is used as precursor for several enzymatic reactions. Of which different forms of NOS induce immunity inflammatory/immunological stimuli in certain tissues and lungs (Virarkar et al. 2013). L-Citrulline enhances NO generation thereby results in the improvement in obese asthmatics (Fernando et al. 2019). Therefore, we have used arginine, citrulline, acetyl citrulline and thiocitrullline as these are produced within the system thereby minimizes secondary complications. In this report, we have explored arginine, citrulline (FDA approved drug), acetyl citrulline and thiocitrullline (experimental stages) for their binding ability with main protease of SARS-COV-2 using molecular docking studies. The rest of the paper is structured as follows. Section 2 presents the Molecular docking studies. Section 3 focuses on results and discussion. Finally, Sect. 4 offers conclusions and future directions.

2 Molecular docking studies

Molecular docking studies were carried out to determine the inhibitory action of *N*-acetyl citrulline, citrulline, thiocitrulline and arginine (ligands), respectively, against the Main Protease (6LU7) of novel coronavirus (COVID-19). The main protease (Mpro) or (3CLPro) of coronavirus is responsible for the viral replication. Thus, the tendency of any of the above ligands (*N*-acetyl citrulline, citrulline, thiocitrulline and arginine) to bind to the active sites of the main protease (3CLpro or Mpro) and thus inhibiting its replication was examined using molecular docking studies. For which, 3CLpro/Mpro structure (6LU7) of COVID-SARS-2 was obtained from protein databank (PDB format (https://www.rcsb.org/) and the structure of ligands (arginine, citrulline, *N*-acetyl citrulline, thiocitrulline) in PDB format was collected from the database of Drug Bank, Canada (https://www.drugbank.ca/). 3CLpro/Mpro structure (6LU7) was prepared by removing all the water molecules so that its active sites (His-41, Cys-145 and Gln-189) can be effectively binds to the different ligands as reported in the literature (Liu et al. 2020; Jin et al. 2020). The active sites were confined in a grid box to compute the binding ability of active sites with ligands. Prior to it, 6LU7 and ligands was optimized, genetic algorithm and Lamarckian algorithm was used in Auto dock tools 1.5.6. The graphical presentations and results were analysed using UCSF Chimera.

3 Results and discussion

Major part of research focus on targeting SARS-COV-2 main protease (Mpro) to prevent its replication. SARS-COV-2 main protease (Mpro) consists of chain containing 306 amino acids classified into three domains. First domain contains 8–101 amino acid residues, and in domain 2, 102–184 aminoacids and in the third 201–303 amino acid residues are present. Domains 2 and 3 are connected by the 185–200 aminoacid sequences in the form of loop. The binding site of SARS-COV-2 main protease are present in domains 1, 2 and the loop (His-41, Cys-145 and Gln-189). There are many reports on the use of molecular docking/in-silico studies to investigate the effectiveness of different types of drugs/molecules to inhibit the replication of the SARS-COV-2 main protease (Mpro). The effective binding of different phytochemicals, biomolecules, drugs and drug-like molecules have been examined and found that majority of the molecules investigated above does not bind to all the active sites effectively (Abu-Saleh et al. 2020; Amin et al. 2020; Basu et al. 2020; Cavasotto and Filippo 2020; Choudhary et al. 2020a, b; Lokhande et al. 2020; Peele et al. 2020; Sharma et al. 2020; Tallei et al. 2020).

Absorption, distribution, metabolism, excretion (ADME) and lower chemical reactivity-related toxicity have to be taken into consideration while selecting the ligands/molecules to bind to the biological receptor. Also higher molecular weight, higher H-bonding properties, lipophilicity and permeability also have to be taken into account prior to the choice of ligands. High-throughput screening of molecules for drugability was generally based on the Lipinski's rule (Lipinski 2000; Lipinski et al. 2001). Therefore, we have

screened and chosen the *N*-acetyl citrulline, citrulline, thiocitrulline and arginine as these molecules have exhibited beneficial effects in enhancement of immune system (Karolina et al. 2015; Lee et al. 2018). In Table 1, the properties of Arginine, citrulline, *N*-acetyl citrulline and thiocitrulline which fullfil Lipinski's five rule are shown. In-silico studies have been carried out to evaluate the potential binding abilities of these ligands (Arginine, citrulline, *N*-acetyl citrulline and thiocitrulline) to main protease (Mpro). Arginine, citrulline, *N*-acetyl citrulline and thiocitrulline were allowed to bind separately to the active sites of SARS COV-2 (3CLpro) using Auto dock 1.5.6. The results of the molecular docking studies have been summarized in Table 2. In Table 2, the structure of different ligands and their lowest binding energies with best conformations by which they bind to the active sites of Mpro is also shown. All the ligands in one or the other conformation have the ability to bind to CYS-145 i.e., one of the active site of main protease thereby exhibiting its ability to inhibit the replication of viral RNA. Of which citrulline also binds to second preferential active site i.e., His-41, while binding, *N*-acetyl citrulline, thiocitrulline and argninine binds to two active sites i.e., His-41 and

Table 1 Properties of drug molecules/ligands (Ref: Drug Bank, Canada: https://www.drugbank.ca/)

	Ligands			
	Citrulline	*N*-Acetyl citrulline	Thiocitrulline	Arginine
Molecular formula	$C_6H_{13}N_3O_3$	$C_8H_{15}N_3O_4$	$C_6H_{13}N_3O_2S$	$C_6H_{14}N_4O_2$
Molecular mass (g mol^{-1})	175.18	217.10	191.25	174.11
LogP	−3.19	−2	−2.6	−3.5
H-bond acceptor count	4	4	3	6
H-bond donor count	4	4	4	5
Rotatable bond count	5	6	5	5

Table 2 Interaction of SARS COV-2 protease with ligands

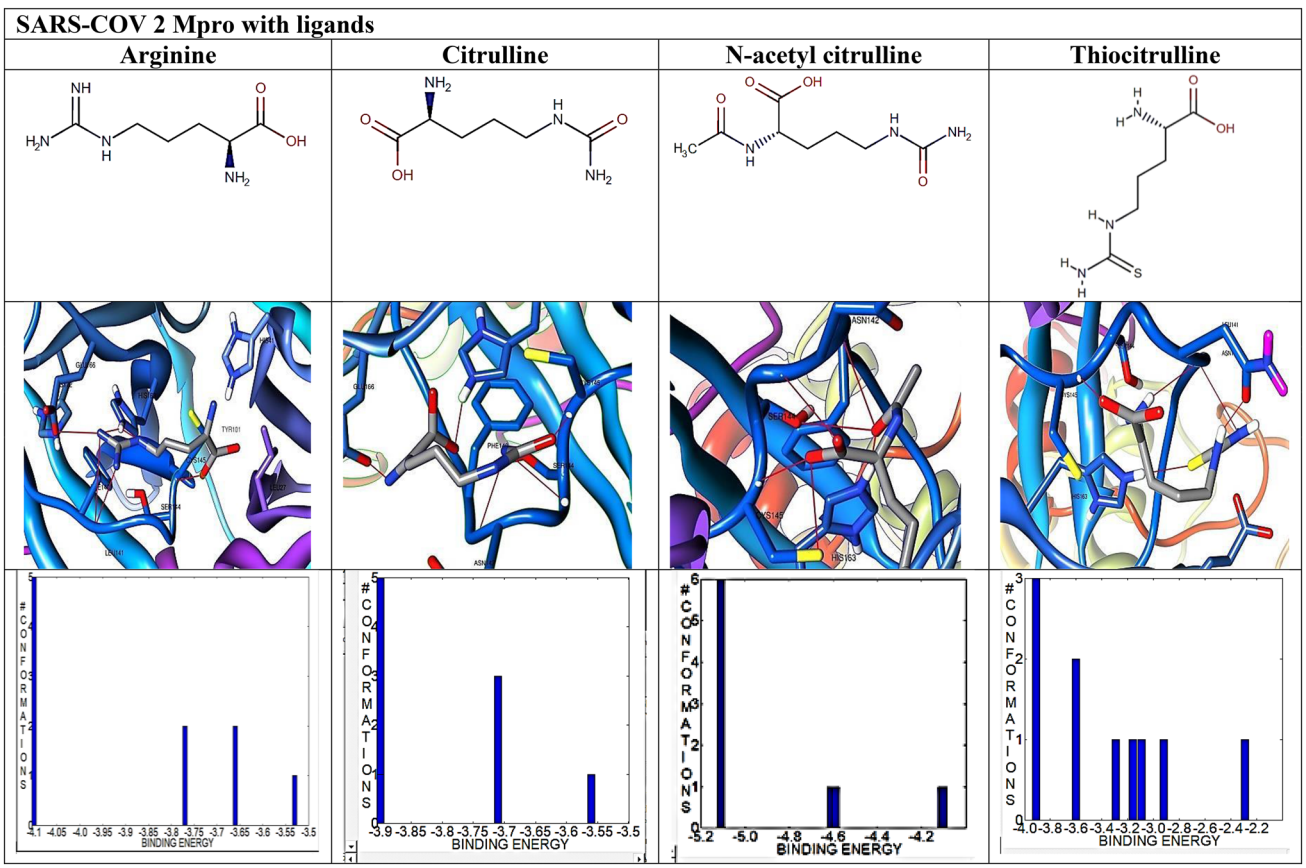

Table 3 Binding energies on interaction of ligands with SARS COV-2 protease

Ligand	Binding energy (kcal mol^{-1})
Citrulline	−3.9
N-Acetyl citrulline	−5.11
Thiocitrulline	−3.91
Arginine	−4.1

Gln-189. Citrulline, *N*-acetyl citrulline and arginine have the tendency to form more number of weaker hydrogen bonds with Mpro. The absence of aromatic groups and long chain of these ligands is an added advantage as they can effectively penetrate and also attach to the other amino acid sites easily. In Table 3, the binding energies of different ligands to active sites of Mpro and their preferences are given. The effectiveness of the ligands to the binding ability to the active sites of Mpro is as follows: *N*-acetyl citrulline > arginine > thiocitrulline > cirulline. Table 4 summarizes the binding energies of different ligands in several conformations with Mpro. Even though individually none of the above ligands bind very effectively to all the target active sites, combination of the above ligands could be better.

There are several reports that COVID-2 can affect other organs in addition to lungs (Amin et al. 2020; Fan et al. 2020). Therefore, it will be difficult to treat in such conditions thereby limiting ourselves to find an alternative. Enhancement of the immunity is one of the best options. Therefore, in addition to the binding affinity, these molecules also have the ability to enhance the immunity of the cells by the generation of nitric oxide in presence of enzymes thereby protecting them. The results show that *N*-acetyl citrulline and citrulline even though are produced during the conversion of arginine, the preferential ability of the former indicates that they can be used as potential supplements during the course of SARS-COVID-2 treatment.

4 Conclusions and future work

Even though in-silico studies demonstrate the preferential binding abilities of FDA approved hydroxychloroquine/redmesveir/niclosamide/azithromycin drugs, in-vivo there are more secondary complications arises due to which their utility has been severely restricted/limited. As an alternative, we have screened and examined arginine, citrulline, *N*-acetyl citrulline and thiocitrulline. Arginine and citrulline has been generated within the system itself thus may have benefits compared to other drugs. Advantage of using the above ligands is in addition to the preferential binding ability to one of the active site of main protease these ligands enhance the immunity. Our results show that arginine, acetyl citrulline and thiocitrullline can also be explored as a supplement in supporting the current treatment procedures adopted for the treatment of SARS-COV-2. Also these molecules have the potential to act as supplements and further in vitro investigations are needed.

Table 4 Interactions of main protease with ligand atoms in best conformation

Ligand	Arginine	Citrulline	*N*-Acetyl citrulline	Thiocitrulline
Binding energy (kcal mol^{-1})	−4.1	−3.9	−5.11	−3.91
Interactions of main protease with ligand atoms	LEU-141 AO:HN; bond distance: 2.906 Å	LEU 141AO:HN bond distance: 2.674 Å	LEU-141A O:O; bond distance: 3.397 Å	PHE-140-AO-H; bond distance: 2.080 Å
	ASN-142-HN:N; bond distance: 3.408 Å	SER 144A OG:HN bond distance: 2.987 Å	GLY-143A-HN:O; bond distance: 2.04 Å	PHE-140-AO:H; bond distance: 2.80 Å
	SER-144A OG:HN; bond distance: 2.851 Å	SER 144A HN:HN bond distance: 2.368 Å	SER-144A OG:O; bond distance: 3.426 Å	LEU-141-AO:H; bond distance: 1.758 Å
	CYS-145 ASG:HN; bond distance: 3.404 Å	CYS-145A HN:O; bond distance: 1.933 Å	CYS-145A HN:O; bond distance: 2.116 Å	ASN-142AO D1-H; bond distance: 1.1971 Å
	CYS-145 ASG:HN; bond distance: 3.408 Å	HIS-163A HE2:O; bond distance: 2.026 Å	CYS-145A SG:HO; bond distance: 3.252 Å	CYS-145-AHN:HO; bond distance: 2.28 Å
	GLU-166 AOE2:HN; bond distance: 3.015 Å	GLU 166 AOE2:HN bond distance: 2.915 Å	HIS-163A HE2:O; bond distance: 1.905 Å	–
	GLU-166 OE1:HN; bond distance: 2.85 Å	–	HIS-164A O:HO; bond distance: 3.225 Å	–

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Declarations

Conflict of interest Author declares no conflict of interest.

Ethical standards This article does not contain any studies involving animals or human participants.

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