International Journal of Chemical Science
www.chemicaljournals.com
Online ISSN: 2523-2843, Print ISSN: 2523-6075
Received: 15-08-2021, Accepted: 01-09-2021, Published: 16-09-2021
Volume 5, Issue 5, 2021, Page No. 5-9

Molecular docking studies on natural and synthetic analogues of curcumin with mprotease for SARS-CoV-2 activating enzyme inhibition

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Abstract
The inhibitory activity of four naturally occurring curcuminoids and 50 synthetic analogues curcumin with Mpro from SARS-CoV-2 using molecular docking are studied. The binding affinity values obtained from docking studies, 2D diagrams of receptor– ligand complex, the nature of interaction between amino acid residues of Mpro with the ligands and surface diagrams indicating effective binding of ligand in the pocket region of protein are presented.

Keywords: SARS-CoV-2, Covid-19, molecular docking, curcuminoids

Introduction

In early 2020, after a December 2019 outbreak in China, the World Health Organization identified SARS-CoV-2 as a new type of corona virus affecting our upper respiratory tract (sinuses, nose, and throat) or lower respiratory tract (lungs). The outbreak quickly spread around the world and to the date, there are no specific medicines for COVID-19 (Kumar and Rathi, 2020) [5]. A large number of drugs are under investigation in different phases of clinical trials, there has been an inherent need to find distinctive antiviral mechanism (Qingxin *et al*, 2020) [9].

Curcumin, an active ingredient in turmeric, and its analogues have been reported to affects multiple molecular targets, implicated with cancer, proliferation, and inflammation (Govindarajan, 1980) [4]. Some curcumin derivatives are very potent antioxidant also (Anand *et al*, 2007) [2]. In this study, we report the binding affinity of some natural and synthetic analogues of curcumin with Mprotein from SARS-CoV-2 and its comparison using docking software (Aaftaab *et al*, 2019) [1]. Molecular docking is used as powerful fastest inexpensive molecular modelling methods in various drug discovery programmes to demonstrate the feasibility of any biochemical reaction as it is carried out before experimental part of any investigation (Leonardo *et al*., 2015) [7]. The ligand receptor binding free energy obtained from molecular docking studies helps to identify ligand conformations adopted within the binding sites of macromolecular targets there by evaluating critical phenomena involved in the intermolecular recognition process (Dar and Mir, 2017) [3].

Materials and Methods

The 3D crystal structure Mprotein/enzyme of SARS-CoV-2 downloaded from PDB (www.rcsb.org). The PDB ID of this proein is 7K3T (DOI**:** 10.2210/pdb7K3T/pdb). The three dimensional structures of curcumin (Compound CID: 969516), demethoxycurcumin (Compound CID: 969516), bisdemethoxycurcumin (Compound CID: 5315472), tetehydrocurcumin (Compound CID: 12 4072) were obtained from PubChem in.sdf format. The three dimensional structures of synthetic analogues of curcumin is derived from chemdraw software in.cdx format and convert to pdb using AVAGADRO software.

Chemical visualization and preparation of protein pdb files f or docking are carried out with EDU PYMOL**.** Auto Dock Tools (ADT) is built on the Python Molecule Viewer (PMV), is used to prepare ligand and receptor (macromolecule) for docking, to define grid for docking, to run a Auto Grid calculation, and to analyze results. LIGPLOT **(**www.uclb.com/technologies/ligplot*)* is is used to generate schematic 2-D representations of protein-ligand complexes from standard Protein Data Bank file input. The output is a colour or black-and-white Postscript file giving simple and informative representation of the intermolecular interactions, including hydrogen bonds and hydophyobic interactions. From DS VISUALIZER, 2D and 3D diagramsindicating H-bond interaction between aminoacid residue and the ligand molecule, aromaticity, charge distribution over ligand-protein complex, hydrophobicity ligand-protein interaction are also obtained (Pratik *et al*, 2020). Autodock Vina molecular docking generate output file with the docking score or binding affinity from which effective drug against COVID-19 can be predicted, a primary step to drug designing (Kumar etal., 2020).

Three sets of ligands were selected for docking studies. They are naturally occurring curcuminoids (Table 1), synthetic analogues of curcumin or 1, 7-diphenyl heptanoids (Table 2) and synthetic analogues of tetrahydrocurcumin or tetrahydro 1, 7-diphenyl heptanoids (Table 3).

Table 1: General structure of ligands – Naturally occurring curcuminoids

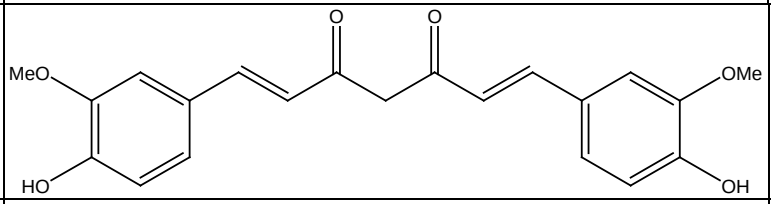
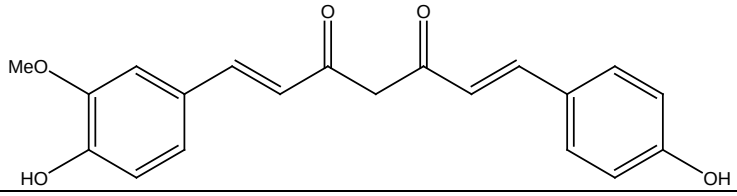
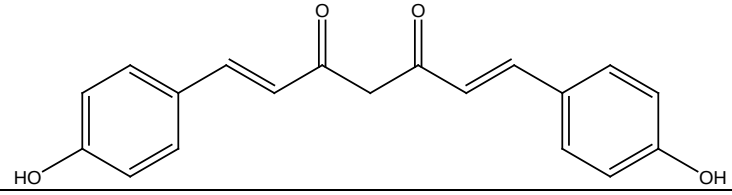
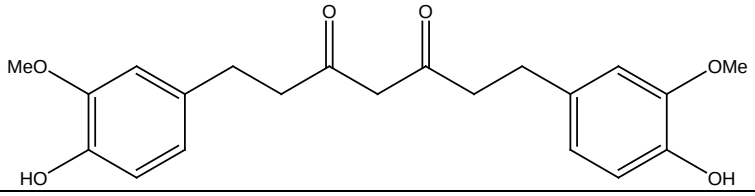
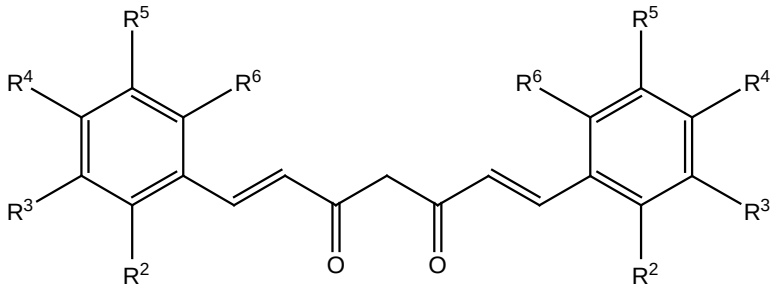
Curcuminoids	Structural Formula (Diketo form)	Binding Affinity (kcal/mol)
Curcumin		-6.9
Demethoxycurcumin		-6.4
Bis(demethoxycurcumin)		-6.5
Tetrahydrocurcumin		-6.5

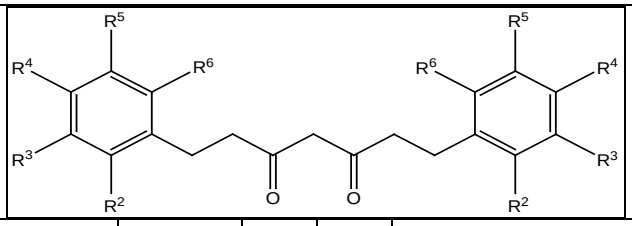
Table 2: General structure of ligands – 1, 7-diphenyl heptanoids



Ligands	R^2	R^3	R^4	R^5	R^6	Binding Affinity (kcal/mol)
[1]	H	H	H	H	H	-6.6
[2]	Cl	H	H	H	H	-6.4
[3]	NO_2	H	H	H	H	-8
[4]	OCH_3	H	H	H	H	-6.3
[5]	OH	H	H	H	H	-5.6
[6]	H	Cl	H	H	H	-5.3
[7]	H	NO_2	H	H	H	-7.8
[8]	H	OCH_3	H	H	H	-6.5
[9]	H	OH	H	H	H	-5.8
[10]	H	H	Cl	H	H	-7.1
[11]	H	H	NO_2	H	H	-8.2
[12]	H	H	OCH_3	H	H	-7.1
[13]	H	H	OH	H	H	-6.5
[14]	OH	OH	H	H	H	-8.1
[15]	OH	H	OH	H	H	-7.2
[16]	OH	H	H	OH	H	-7.3
[17]	OH	H	H	H	OH	-6.6
[18]	H	OH	OH	H	H	-7.4
[19]	H	OH	H	OH	H	-7.2
[20]	OH	OH	OH	H	H	-8.8
[21]	OH	OH	H	OH	H	-7.3
[22]	OH	OH	H	H	OH	-8.9
[23]	OH	H	OH	OH	H	-7.5
[24]	OH	H	OH	H	OH	-7.2

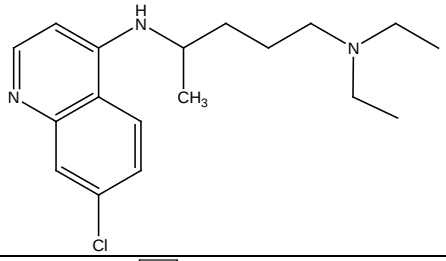
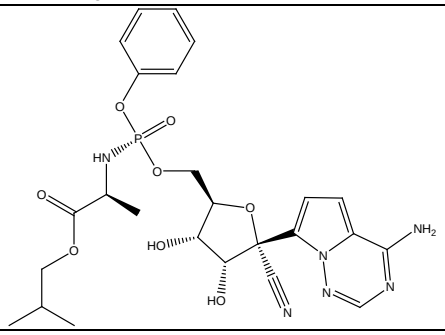
[25]	H	OH	OH	OH	H	-8.7

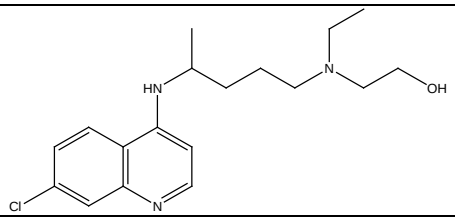
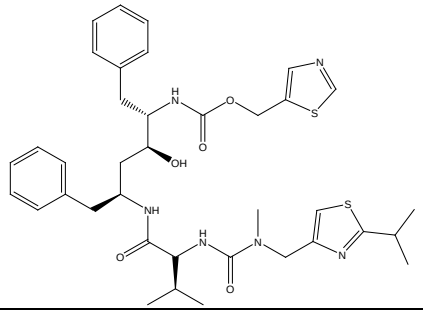
Table 3: General structure of ligands –Tetrahydro 1, 7-diphenyl heptanoids



Ligands	R^2	R^3	R^4	R^5	R^6	BINDING AFFINITY (kcal/mol)
[26]	H	H	H	H	H	-7.3
[27]	Cl	H	H	H	H	-5.9
[28]	NO_2	H	H	H	H	-5.8
[29]	OCH_3	H	H	H	H	-6.3
[30]	OH	H	H	H	H	-6
[31]	H	Cl	H	H	H	-5.8
[32]	H	NO_2	H	H	H	-7.1
[33]	H	OCH_3	H	H	H	-5.5
[34]	H	OH	H	H	H	-6.4
[35]	H	H	Cl	H	H	-6.9
[36]	H	H	NO_2	H	H	-7.7
[37]	H	H	OCH_3	H	H	-7.1
[38]	H	H	OH	H	H	-7.4
[39]	OH	OH	H	H	H	-7.2
[40]	OH	H	OH	H	H	-6.8
[41]	OH	H	H	OH	H	-6.4
[42]	OH	H	H	H	OH	-6.3
[43]	H	OH	OH	H	H	-7
[44]	H	OH	H	OH	H	-7.9
[45]	OH	OH	OH	H	H	-8.2
[46]	OH	OH	H	OH	H	-8.4
[47]	OH	OH	H	H	OH	-8
[48]	OH	H	OH	OH	H	-7
[49]	OH	H	OH	H	OH	-8.6
[50]	H	OH	OH	OH	H	-8.5

Table 4: Some antiviral drugs against COVID-19

Ligands	Structure	Binding Affinity kcal/mol
Chloroquine		**-5.9**
Remdesivir		**-7.3**

Hydroxychloroquine		**-5.5**
Ritonavir		**-7.3**

Results and Discussion

Docking studies were performed with all the 54 ligands and binding affinity values obtained are tabulated in tables 1-3. The binding affinity values (Sanjay *et al*., 2020) [10] obtained were ranging from -5.5 to -8.7 kcalmol^{-1}, which is comparable to those of clinically used drugs against COVID-19. Among the naturally occuring curcuminoids, highest value for binding affinity was obtained for curcumin indicating that curcumin is most potent for the receptor Mprotease. Both groups showing +M effect (hydroxy, methoxy, chloro groups) and groups showing -M effect (nitro group) were found to have higher binding affinity than unsubstituted compounds. Disubstituted curcumin analogues (symmetric) with hydroxy group at phenyl ring in 2, 3 position has maximum binding affinity (-8.1 kcal/mol) than other five positional isomers. This trend varies in tetrahyadroderivatives, 3, 5 substituted has maximum value (-7.9) kcal/mol). Curcumin analogues having trihydroxy substituted phenyl rings have larger binding affinity than those having dihydroxy substituted phenyl rings. Curcumin analogue having 2, 3, 6- trihydroxy phenyl rings have -8.9 kcal/mol of binding affinity and the tetrahydrocurcumin analogue having 2, 4, 6- trihydroxy phenyl rings have -8.6 kcal/mol of binding affinity. A comparison of binding affinity values of these ligands with clinically used drugs against COVID-19 reported in the literature is included in Table 4. Remdesivir, it is largely used to treat corona patients, having binding affinity -7.3 kcal/mol with Mprotease. It is interesting to note that some of the curcumin analogues have more binding affinity values than these clinically used drugs.

Binding of natural and synthetic analogues of curcumin with proteins are mainly hydrogen bonding, van der Waals forces, pi alkyl bonding, pi suiphur bonding etc. The binding affinity increase with increasing in bonding interactions. Most of the amino acid residues shows van der Waals interaction with ligands. These attractions do not result from a chemical electronic bond, they are comparatively weak and therefore more susceptible to disturbance. The van der Waals force quickly vanishes at longer distances between interacting molecules.

Protein- target structures and active amino acid sites obtained for curcumin using the software Biovia Discovery Studio, Edupymol and Ligplot are shown in Figure 1. In the case of other ligands, the results obtained are very similar in nature and hence they are not presented here.

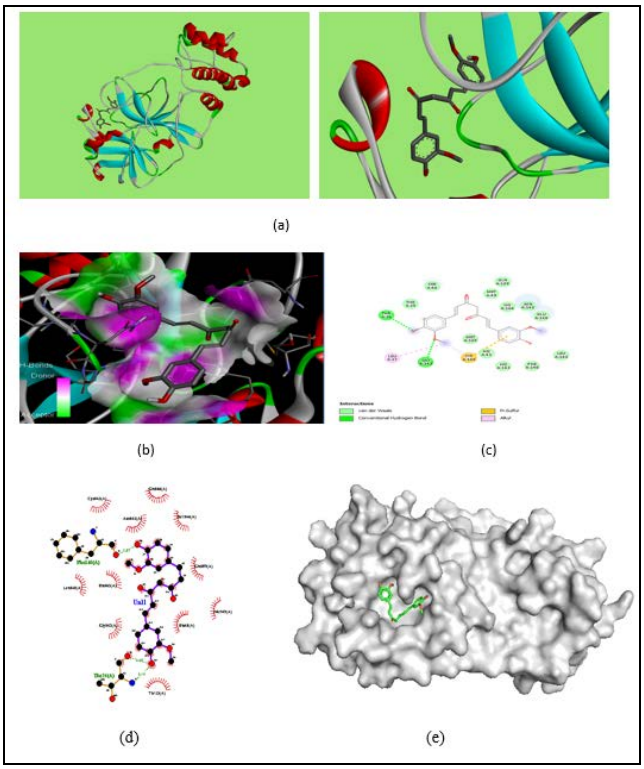


Fig 1: Protein- target structures and active amino acid sites obtained for curcumin using the software (a) Biovia Discovery Studio (b) hydrogen bond interactions from biovia discovery Studio (c) 2D plot with interacting aminoacids and types of interactions (d) LIGPLOT 2D showing the nature of interactions and (e) surface structure from Edu Py Mole showing ligand occuping in the pocket region of protein

Conclusion

There is an urgent need to explore new therapeutic compounds which will offer safer, easily available, efficacious and cost effective treatment for COVID-19. In this study, naturally occurring curcuminoids and synthetic analogues of curcumin were explored to inhibit coronavirus protein activities. 54 ligands were screened for their binding efficiency on Mprotease COVID-19 (SARS-CoV-2) using computational docking studies. Methoxy and chloro substituted have lesser binding score. Synthetic curcumin analogues having nitro group in phenyl rings and those having trihydroxy substituted phenyl rings has maximum binding affinity towards Mprotease. These have comparable

or more binding affinity than the clinically used drug against coronaviruses such as remdesivir and ritonavir. These studies are expected to provide useful insights into the roles of various substitution patterns on the curcumin derivative and also help to design more potent compounds. Our studies reveal that many synthetic analogues of curcumin are potential agents to inhibit Mprotease from SARS-CoV-2. Further studies in this direction may lead to the development of effective drugs to treat COVID 19 in future.

Acknowledgement
PV and SK thank Principal, SNGS College Pattambi for the encouragement and support.

Funduing Source
This research did not receive any specificgrant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest
There is no conflict of interest associated with the authors of this paper.

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