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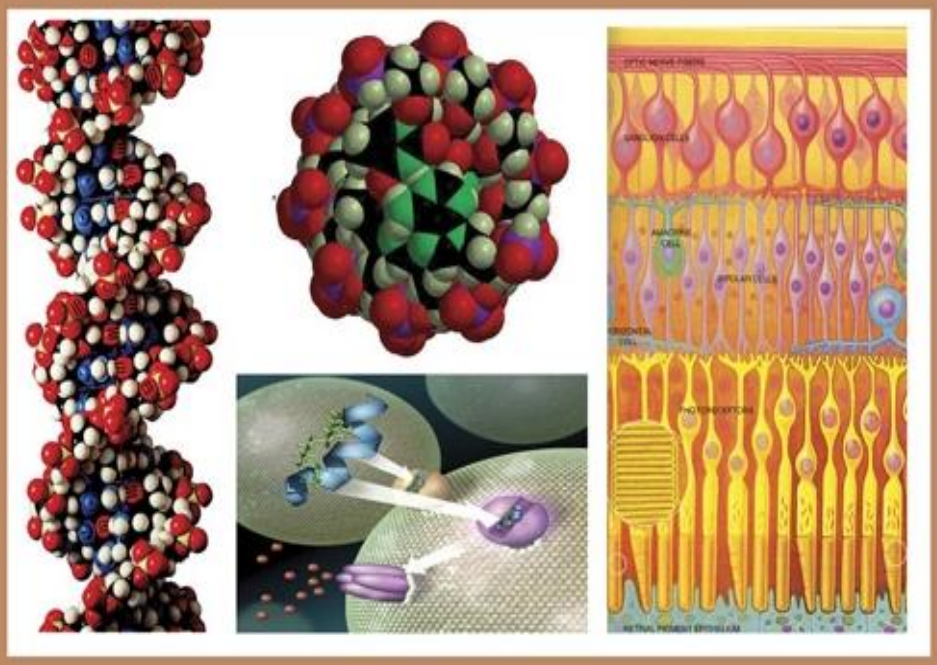

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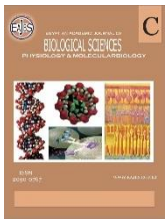

Antiviral Effect of Curcuminoids and Curcumin Derivatives Against Coronavirus (Sars-Cov-2) Predicted Using Molecular Docking Approach

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ABSTRACT

SARS-CoV-2 is a newly emerging pandemic circulating worldwide causing millions of infections and many thousands of deaths. There are currently no specific therapies for treating coronavirus infections. Structure and screening results of important targets such as 3-chymotrypsin-like protease ($3CL^{pro}$) were thoroughly discussed. It is well known that curcumin and turmeric extracts showed prominent anti-inflammatory, antiviral, antibacterial and anti-fungal activities, moreover they showed a positive effect on cytokine storm in many earlier studies. In the present study, with the aid of the molecular docking approach, we identify new possible inhibitors of SARS-CoV-2 using curcuminoids and curcumin derivatives. The identification of the M^{pro} protease structure in COVID-19 provides a valuable chance to develop potential drug candidates for treatment. Considering the main protease in CoVs ($3CL^{pro}$) (PDB ID 6LU7) and docking of our molecules in addition to some drugs for comparison purposes were carried out using the Molegro virtual docker. Curcuminoids and curcumin derivatives docked into 6LU7 active site revealed lower energy scores indicating more favored protein-ligand complexes. Curcuminoids and five curcumin derivatives showed to have the best potential to act as COVID-19 possible treatment. Further, *in vitro* and *in vivo* studies are necessary to examine their medicinal use for the identified molecules against coronavirus infection.

INTRODUCTION

A new coronavirus (CoV) identified as COVID-19 virus is the etiological agent responsible for the 2019-2020 viral pneumonia outbreak that commenced in Wuhan, China and spread worldwide (Zhu et al., 2020, Li et al., 2020, Zhou et al., 2020 and Wu *et al.,* 2020). The recent pandemic of SARS-CoV-2 has required urgent treatments for numerous patients. No vaccines or antivirals are available for COVID-19. The efficacy against COVID-19 of WHO antiviral treatments of choice, which were developed for other pathologies, is controversial. Hence, alternative approaches are required.

Turmeric (*Curcuma longa* L) is in the family of Zingiberaceae and the most common synonyms for it are *Curcuma domestica* Vale‹*Curcuma domestica* Loir, *Amomum curcuma* Jacq, curcuma, yellow root, Indian saffron, and yellow ginger. It is native to India and Bangladesh and is cultivated in Pakistan, and many other countries. Turmeric contains 1.5–5% volatile oil, mainly 60% turmerone and 25% zingiberene. It contains curcuminoids (2.5–8%) which are responsible for the yellow color. Particularly, three curcuminoids, namely curcumin (diferuloylmethane) (71.50–94%), demethoxycurcumin (6–19.4%), and bisdemethoxycurcumin (0.3–9.10%) are responsible for the yellow color (Shahidi and Hossain). The chemical structures of the most abundant compounds found in turmeric are shown in figure one.

Curcumin offers a wide variety of medicinal value and a great range of preventive beneficial effects in many illnesses, according to growing data. Curcumin has been studied on lung fibrosis in several experimental animal models, and these investigations show that curcumin reduces lung damage and fibrosis induced by radiation, chemotherapeutic agents, and toxicants. An increasing evidence from pharmacological and animal studies supports the idea that curcumin protects against chronic obstructive pulmonary disease, acute lung injury, acute respiratory distress syndrome, and allergic asthma, with its therapeutic action focusing on the prevention or modulation of oxidative stress and inflammation. These findings provide support to the potential of evaluating curcumin in individuals suffering from lung conditions (Venkatesan *et al.*, 2007).

Curcumin antiviral activity was observed against many different viruses including hepatitis viruses, influenza viruses and emerging arboviruses like the Zika virus (ZIKV) or chikungunya virus (CHIKV). Interestingly, it has also been reported that the molecule inhibits human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2) and human papillomavirus (HPV). Many *in vitro* and *in vivo* studies indicated that curcumin is active against different fungi and bacteria, including even highly pathogenic, emerging and multi-drug-resistant strains (Praditya *et al.*, 2019). It was documented that curcumin is effective in inhibiting numerous cytokines, as well as its effectiveness in the animal models of diseases and disorders linked with cytokine storm, imply that it may be beneficial in the treatment of Ebola and patients with cytokine storm. Numerous cytokines, both proinflammatory such as interleukin-1 (IL-1), IL-6, tumor necrosis factor- (TNF), and anti-inflammatory (IL-10), are produced during cytokine storm, leading in hypotension, bleeding, and, eventually, multiorgan failure. The cytokine storm is most commonly linked with the H1N1 influenza pandemic, bird flu H5N1 infection, and, more recently, the SARS-CoV-2 pandemic (Sordillo and Helson, 2015).

Curcumin has antioxidant, anti-inflammatory, anti-cancer, anti-metastasis, angiogenesis inhibitor, neuroprotective, cardioprotective, nephroprotective, and hepatoprotective activities (Aggarwal *et al.*, 2007). It is well known that curcumin is very safe even at high oral doses and extensively used in food industry in different parts of the world, its broad-spectrum anti-infective activity makes it a promising drug candidate (Praditya *et al.*, 2019). Herein, we examine the power of curcumin and for the first time semi-synthetic curcumin compounds as potential inhibitor candidates for SARS-CoV-2 using $3CL^{pro}$ (PDB ID 6LU7) in molecular docking investigation.

MATERIALS AND METHODS

The crystal structure of the molecular target, protease enzyme (COVID-19 $3CL^{pro}$ (PDB ID: 6LU7), was

retrieved from RCSB protein data bank (https://www.rcsb.org/strcture/6LU7) (https://www.rcsb.org/strcture/6LU7. Last accessed on 5/5/2020) (see table 1). For the molecular docking study, drugs, herbal molecules (such as curcumin) and semi-synthetic compounds of curcumin have been included in the current study. The two-dimensional chemical structures of molecules were prepared through ChemSketch software. The three-dimensional chemical structures of the investigational ligands were designed and optimized for energy minimization and saved in. mol format subsequently converted into .pdb format by Hyperchem software 8.1. Before starting the molecular docking process, targets are modified for removal of water molecules and native ligands attached to the target and other heteroatoms which may provide hindrance in the simulation. Besides, hydrogen atoms were added into the target (Agrawal et al., 2020). These all processes were carried out in the Molegro virtual docker windows execution file. Ligands used herein are shown in figures 1 & 2.

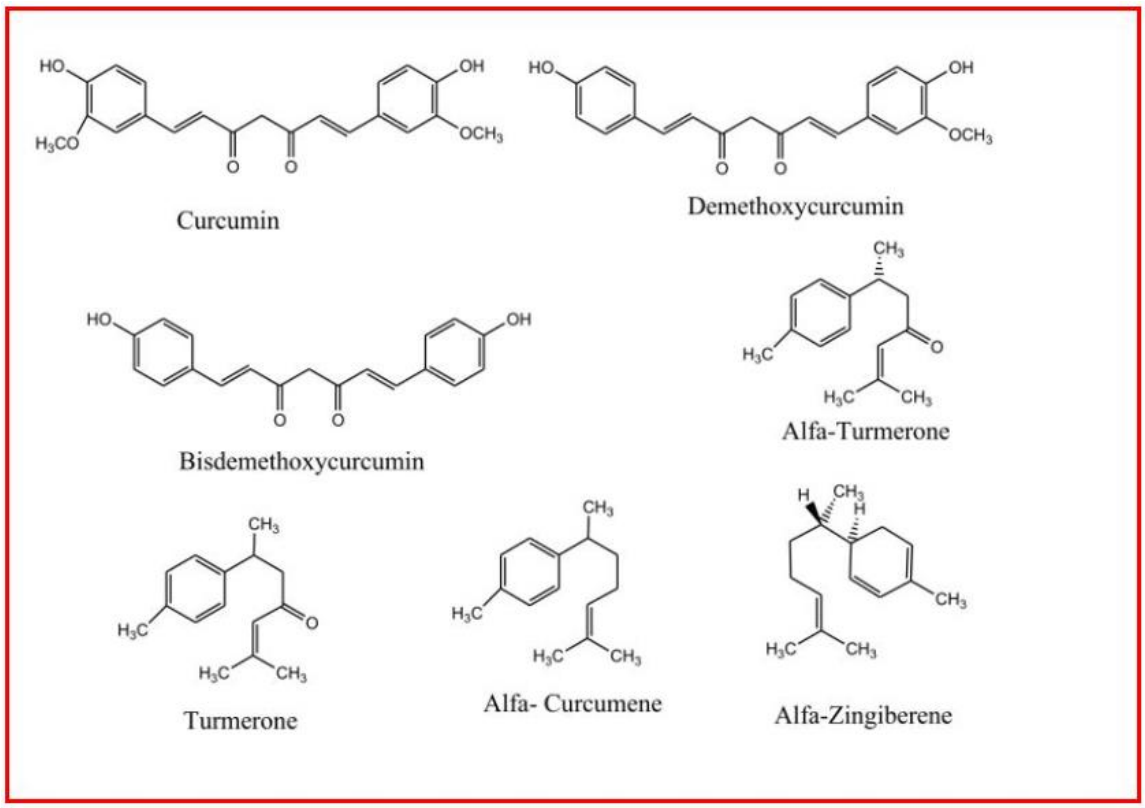

Fig. 1: Major chemical constituents of turmeric.

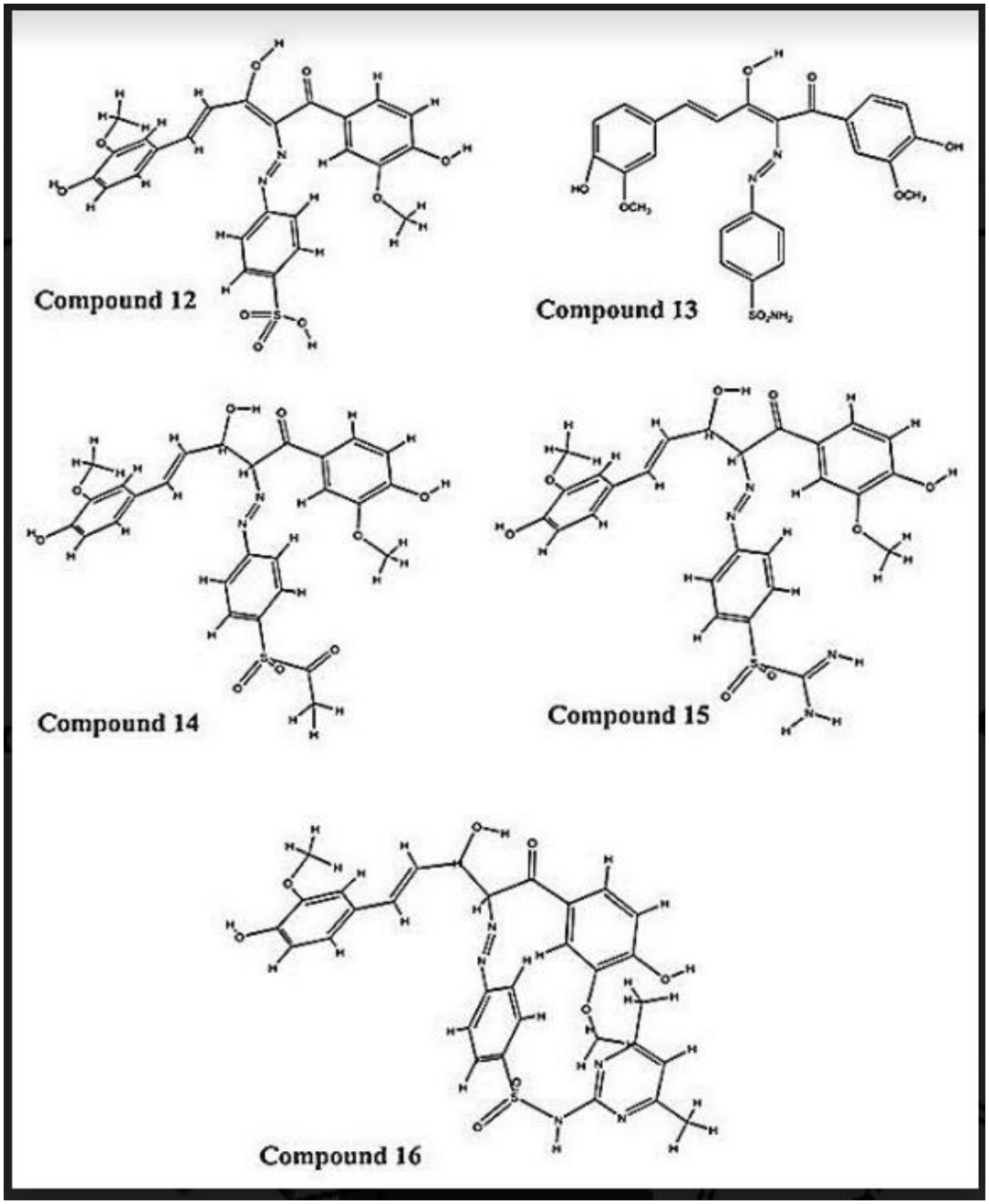

Fig. 2: Structure of semi-synthetic curcumin compounds

RESULTS

The present molecular docking study was carried out to quantify the energy of the curcumin, demethoxycurcumin, bisdemethoxycurcumin, and curcumin derivatives as ligands to interact with COVID-19 main protease enzyme coded as 6LU7 (Table 1) in comparison with drugs that are used in the management of those patients such as chloroquine, hydroxychloroquine, favipiravir, and remdesivir.

Table 1: Crystallographic properties of enzyme

Enzyme	PDP code	Classification	Organism	Expression system	Resolution	Method	Total structure weight (DA)	Chain
Covid-19	6LU7	Viral Protein	Bat SARS-Like coronavirus	*Escherichia coli* BL21DE3	2.16Å	X-Ray Differaction	34506.34	A

The lower MolDock score showed that ligand enzyme interaction was more stable. The results showed that the curcumin has -158.27 kcal/mol, demethoxycurcumin -151.45 kca/mol, bisdemethoxycurcumin-149.34 kca/mol. Curcumin derivatives (12, 13, 14,15, and 16) showed the lowest MolDock scores. Remdesivir was the lowest compared with chloroquine, hydroxychloroquine, and favipiravir (Table 2).

Table 2: The investigated ligands and their properties, MolDock score, protein-ligand interactions, hydrogen bonds energy.

Ligand	Molecular Weight	Area (Å²)	Volume (Å³)	MolDock Score	Protein ligand interactions	Hydrogen bonds energy (Kcal/mol)
Favpiravir (Avigan)	158.1	292.54	424.32	-65.45	-75.47	-2.99
Remdesivir	579.56	863.27	1527.96	-164.81	-188.52	-6.32
Chloroquine	329	564.9	983.04	-123.62	-135.43	-6.32
Hydroxychloroquine	335.87	578.57	1009.73	-116.17	-131.60	-4.93
Curcumin	370.39	663.65	1088.76	-158.27	-163.98	-10.61
Alfa-Curcumin	202.30	427.26	726.6	-79.47	-86.197	0
Alfa-Tumerone	217	431.48	736.48	-102.42	-106.45	-7.79
Alfa- Zingiberene	205.36	429.42	731.56	-96.83	-103.62	0
Bisdemethoxcurcumin	310.34	575.56	936.12	-149.34	-154.16	-13.54
Demethoxycurcumin	340.37	624.04	1013.56	-151.45	-143.68	-12.74
Turmerone	218.33	443.53	750.56	-95.28	-101.96	- 2.07
Curcumin derivative 12	528.53	763.28	1349.19	-181.71	-170.78	-17.78
Curcumin derivative 13	529.56	788.51	1382.58	-197.64	-165.6	-15.8
Curcumin derivative 14	556.58	815.96	1445.1	-176.80	-178.34	-10.88
Curcumin derivative 15	556.59	820.0	1452.8	-167.41	-182.25	-9.36
Curcumin derivative 16	634.68	824.23	1579.16	-195.33	-202.61	-13.29

Docking analysis showed that the powerful H-bonds that interact with 6LU7 amino acids in the COVID-19 $3CL^{pro}$ active site. The binding energy results are related to the number of H-bonds formed with the active site pocket of COVID-19 $3CL^{pro}$. The active sites of SARS-CoV-2 6LU7 protein exist within the key amino acids such as CYS145, HIS163, HIS164, MET165, GLU166, LEU167. The bonds of ligands to the receptor are shown in detail (Figs. 3-19).

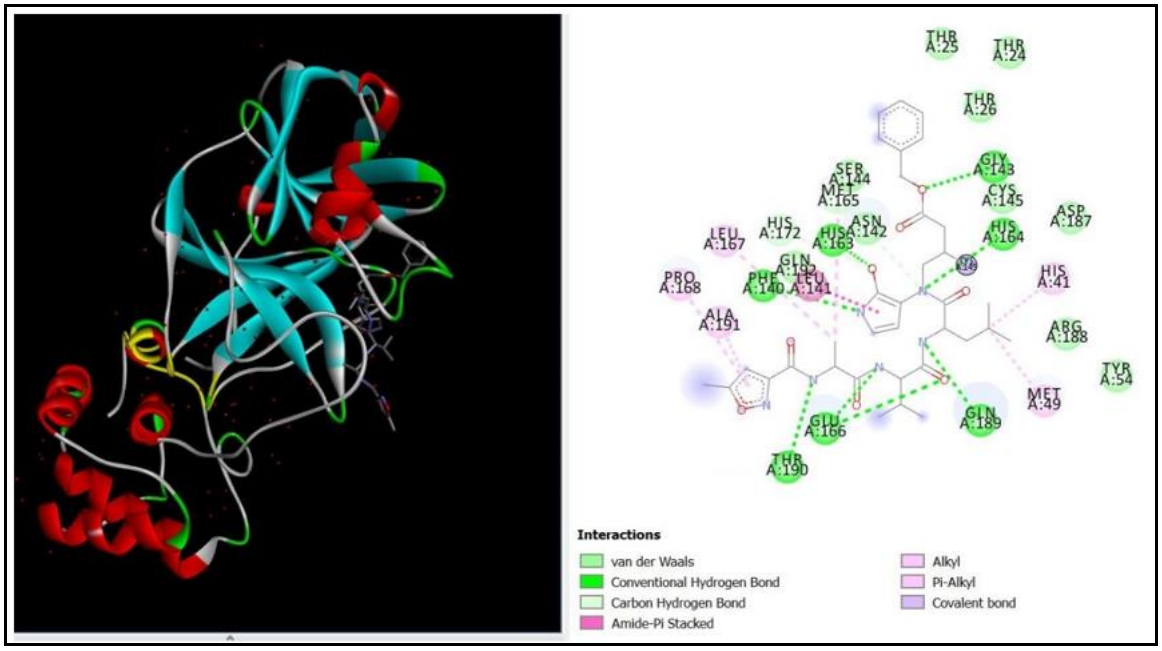

Fig. 3: The active sites of SARSCoV2 6LU7

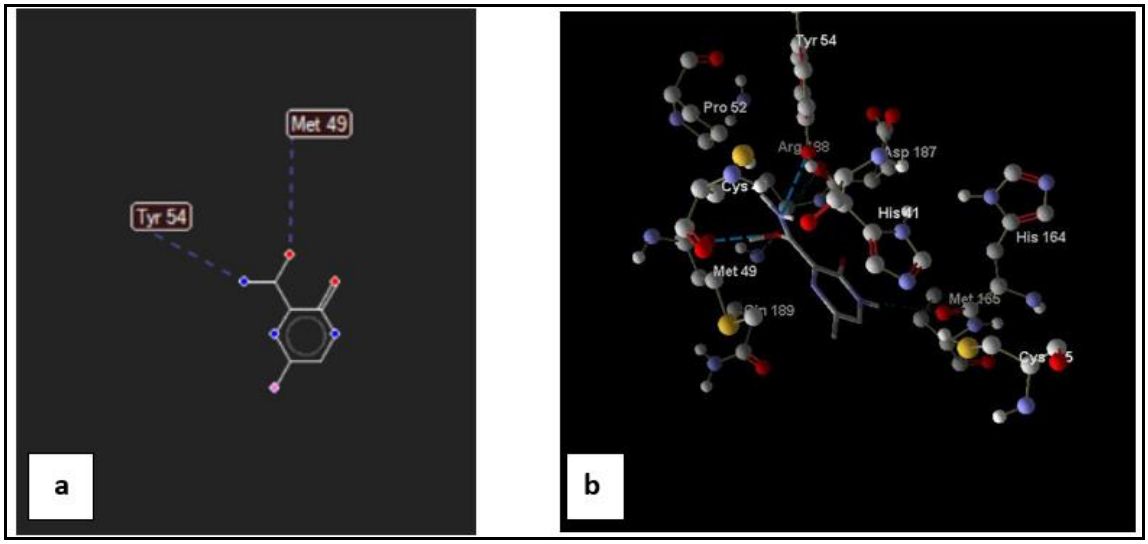

Fig. 4: 2D (a) and 3D (b) diagrams: interaction between favpiravir (avigan) and (6LU7). Amino acid Tyr54 (donor rotatable) with distance about 2.67Å and energy of -2.5 k cal/mol. Amino acid Met49 (donor rotatable) with distance about 2.91Å and energy of -2.5k cal/mol.

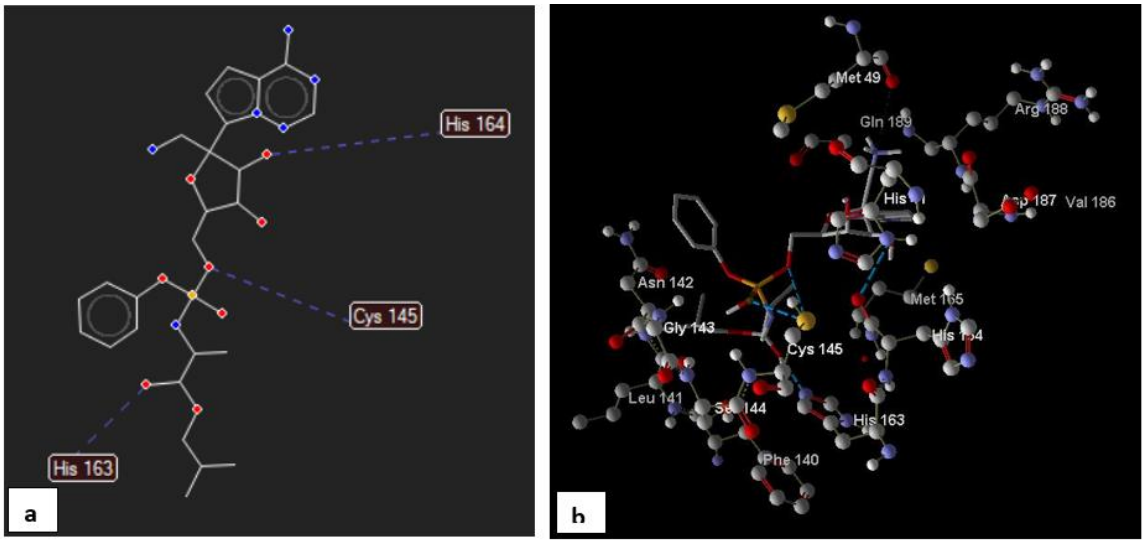

Fig. 5: 2D (a) and 3D (b) diagrams: interaction between remdesivir and (6LU7). Hydrogen interaction are possible with: Amino acid His163 (donor rotatable) with distance about 2.63 Å and energy of -2.5 k cal/mol. Amino acid His164 (donor rotatable) with distance about 3.1Å and energy of -2.48 k cal/mol. Cys145 formed two hydrogen bond; i- Cys145 (donor rotatable) with distance about 2.63 Å and energy of-2.5 K cal/mol. ii- Cys145 (donor rotatable) with distance about 3.23 Å and energy of-1.8 K cal/mol. Amino Acid Thr190 (donor rotatable) with distance 3.11 Å and energy of -2.45 K cal/mol.

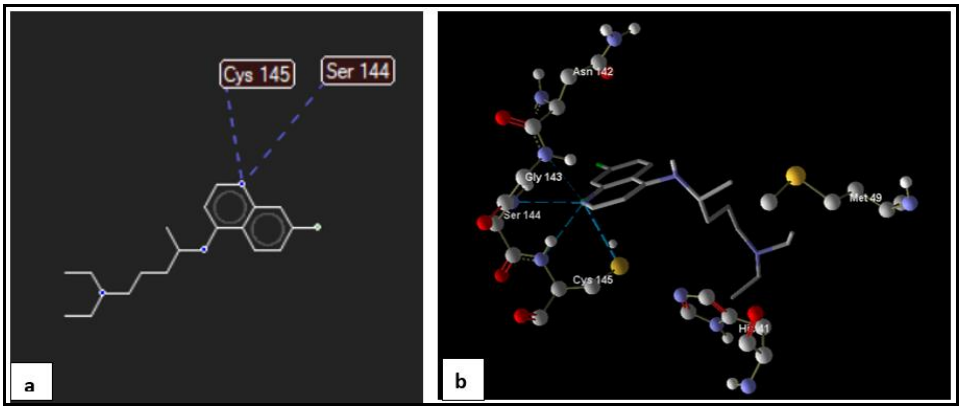

Fig. 6: 2D (a) and 3D (b) diagrams: interaction between Chloroquine and (6LU7). Amino acid Cys145 by (two H-donor) with distance about 3.15, 3.02Å and energy of -2.24, -1.33 kcal/mol. Amino acid Ser144 (H-donor) with distance about 3.12Å and energy of -1.13 k cal/mol.

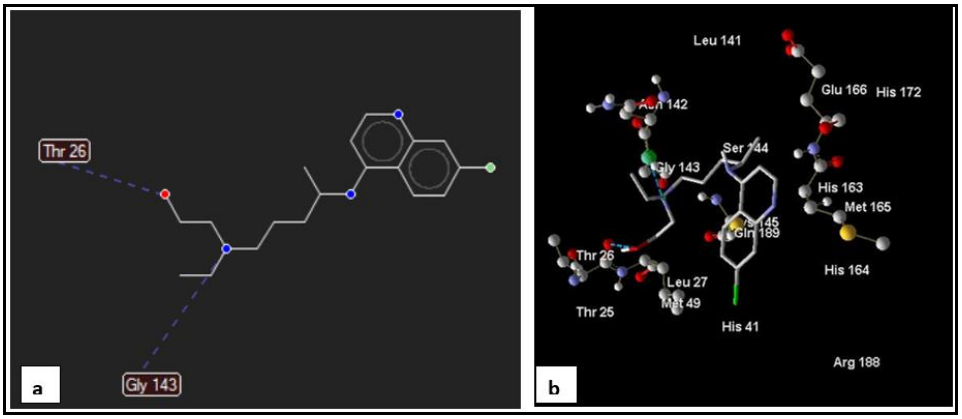

Fig. 7: 2D (a) and 3D (b) diagrams: interaction between hydroxychloroquine and (6LU7). Amino acid Thr26 (donor rotatable) with distance about 3.10Å and energy of -2.5k cal/mol. Amino acid Gly143 (H-donor) with distance about 2.78Å and energy of -2.43 k cal/mol.

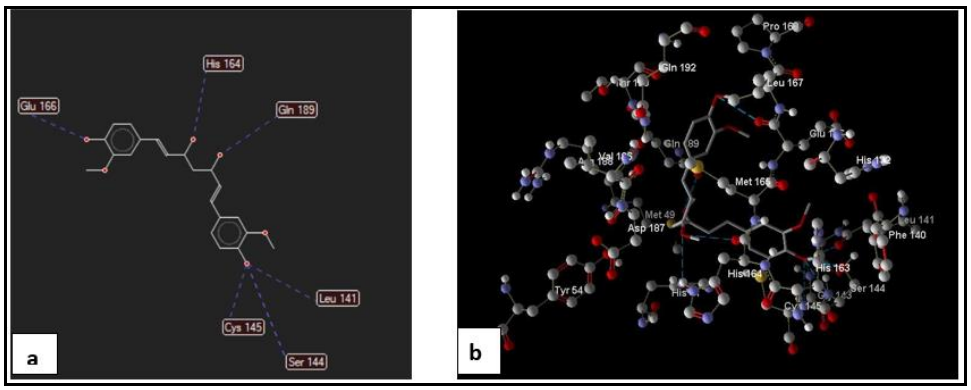

Fig. 8: 2D (a) and 3D (b) diagrams: interaction between Curcumin and (6LU7). Five Hydrogen interaction are possible with: Amino acid Glu166 (donor rotatable) with distance about 3.2 Å and energy of -1.92 k cal/mol. Amino acid His164 (H donor rotatable) with distance about 3.32Å and energy of -1.40 k cal/mol. Ser144 (H donor rotatable) with distance about 3.1 Å and energy of -2.5 K cal/mol. Amino Acid Gln189 (donor rotatable) with distance 2.98Å and energy of -2.5 K cal/mol. Amino Acid Cys145 (H-Acceptor) with distance 3.3Å and energy of -0.84 K cal/mol.

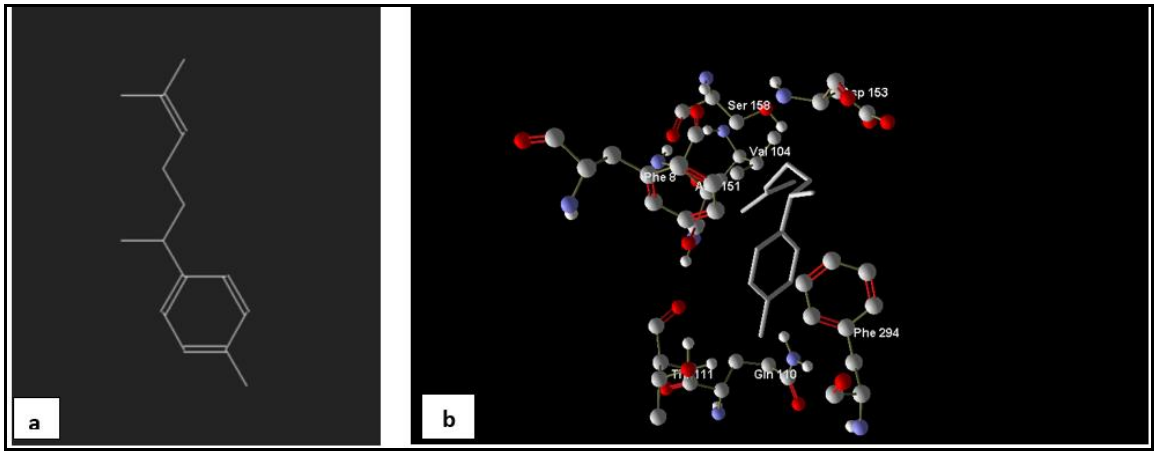

Fig. 9: 2D (a) and 3D (b) diagrams: interaction between Alfa-Curcumin and (6LU7).No perceptible interactions, only electrostatic exist (Van der Waals).

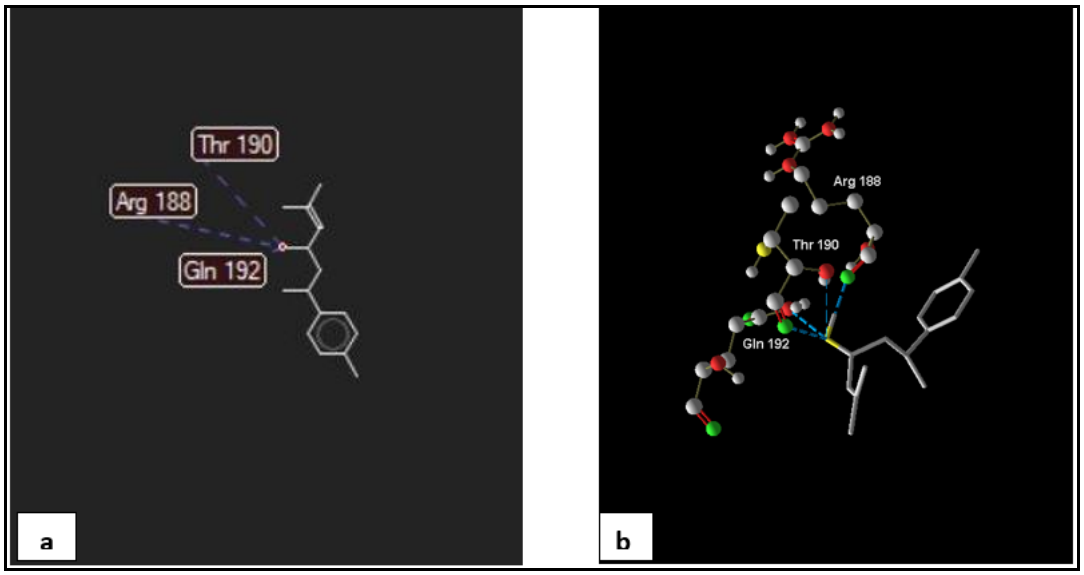

Fig. 10: 2D (a) and 3D (b) diagrams: interaction between Alfa-Tumerone and (6LU7). Amino acid Gln192 (donor rotatable) with distance about 2.63 Å and energy of -2.5 k cal/mol. Amino acid Arg188 (donor rotatable) with distance about 2.73Å and energy of -2.5 k cal/mol.

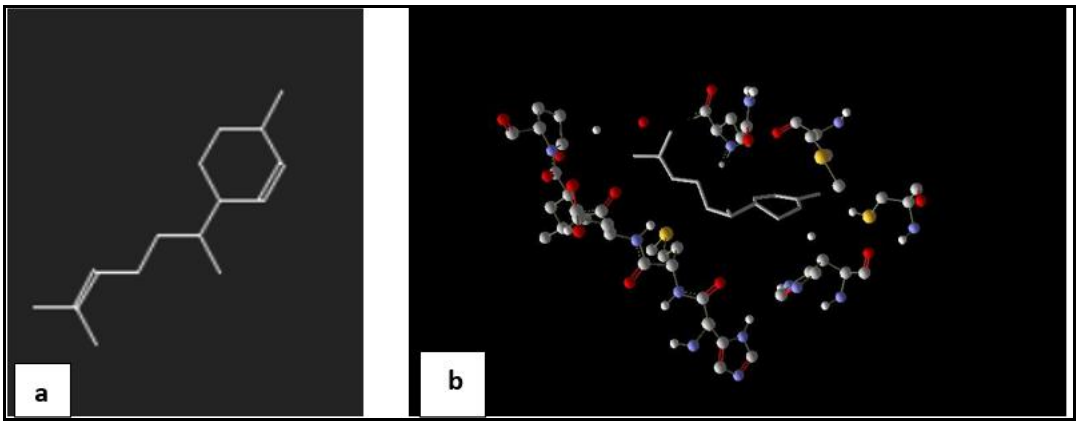

Fig. 11: 2D (a) and 3D (b) diagrams: interaction between Alfa- Zingiberene and (6LU7). No perceptible interactions, only electrostatic exist (Van der Waals).

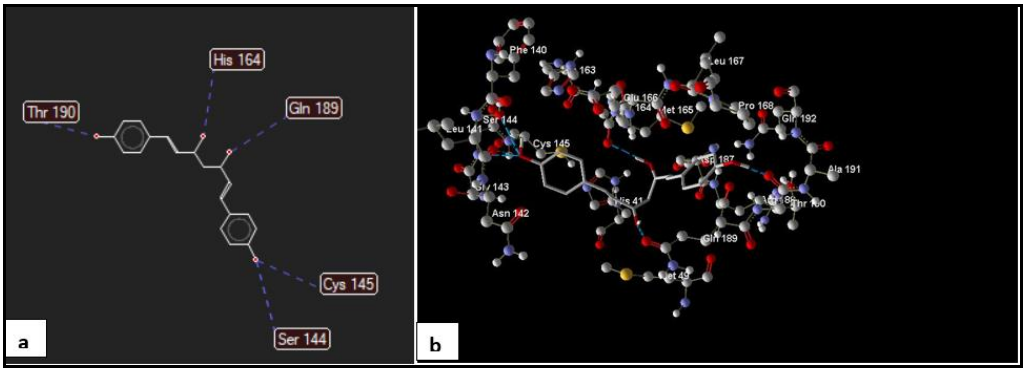

Fig. 12: 2D (a) and 3D (b) diagrams: interaction between bisdemethoxcurcumin and (6LU7). Amino acid Thr190 (donor rotatable) with distance about 2.73 Å and energy of -2.5 k cal/mol. Amino acid His164 (donor rotatable) with distance about 3.16Å and energy of -2.18 k cal/mol. Gln189 (donor rotatable) with distance about 2.80 and energy of -2.5 K cal/mol. Amino Acid Cys145(H-acceptor) with distance 3.25 Å and energy of -0.76 K cal/mol. Amino Acid Ser144(donor rotatable) with distance 2.76 Å and energy of -2.5K cal/mol.

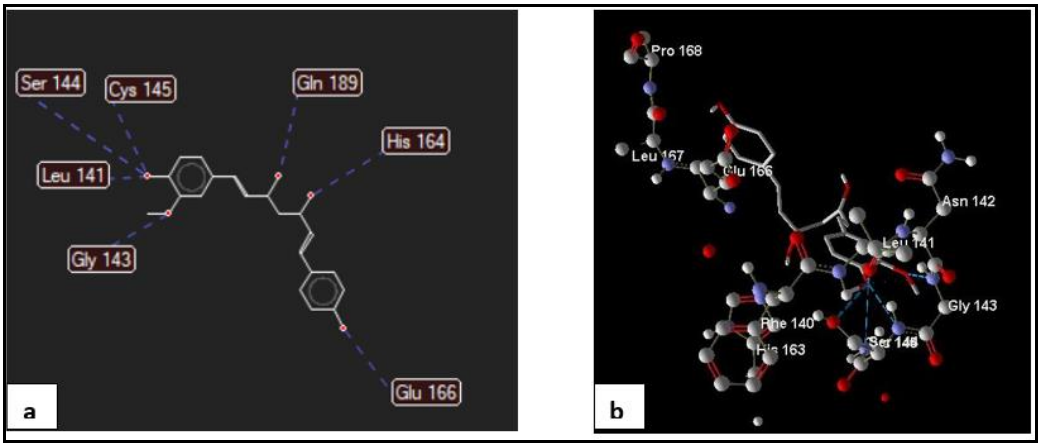

Fig. 13: 2D (a) and 3D (b) diagrams: interaction between demethoxycurcumin and (6LU7). Many hydrogen bond interaction are possible with: Amino acid Ser144 (donor rotatable) with distance about 2.94 Å and energy of -2.50 k cal/mol. Amino acid Cys145 (H-Acceptor) with distance about 3.17Å and energy of -1.15 k cal/mol. Amino Acid Gly143(H-donor) with distance 2.86 Å and energy of -2.14 K cal/mol. Amino Acid Glu189(H-donor) with distance 2.88 Å and energy of -2.5 K cal/mol. Amino Acid His164 (H-donor rotatable) with distance 3.17 Å and energy of -2.16K cal/mol. Amino Acid Glu166(H-donor) with distance 3.17 Å and energy of -1.70K cal/mol.

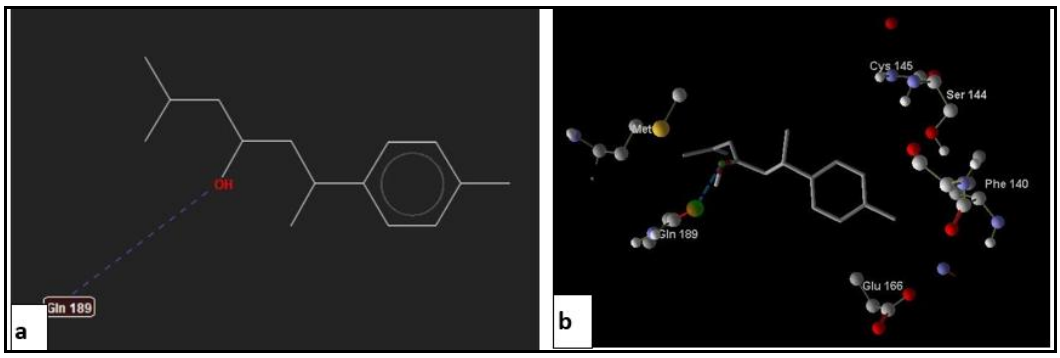

Fig. 14: 2D (a) and 3D (b) diagrams: interaction between turmerone and (6LU7). Amino Acid Gln189 (donor rotatable) with distance 2.65 Å and energy of -2.07 K cal/mol.

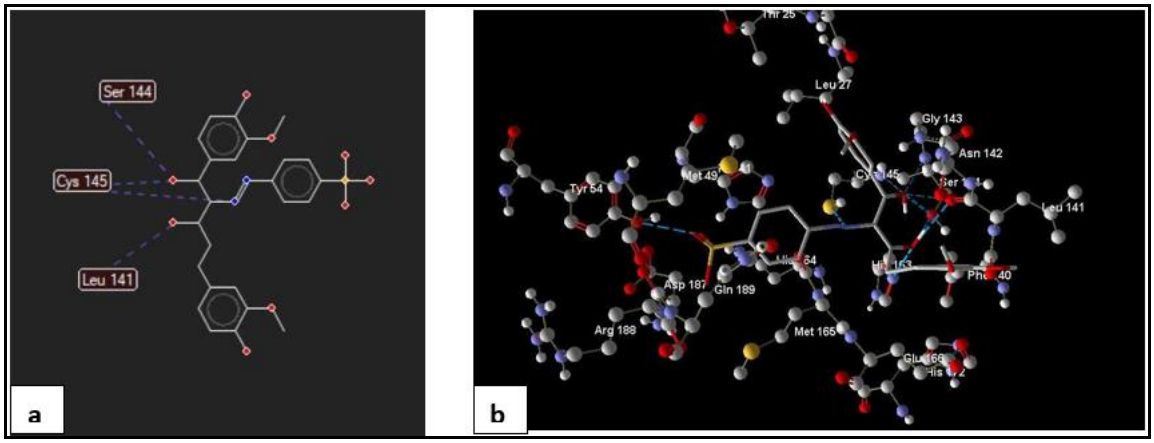

Fig.15: 2D (a) and 3D (b) diagrams: interaction between and curcumin derivative 12 and (6LU7). Amino Acid His163(H-donor) with distance 2.78Å and energy of -2.5 K cal/mol. Amino Acid Leu141 (H-donor) with distance 3.04 Å and energy of -2.5 K cal/mol. Amino Acid Cys145 (H-donor) with distance 2.95 Å and energy of -2.5 K cal/mol. Amino Acid Cys145 (H-Acceptor) with distance 3.12 Å and energy of -1.08 K cal/mol. Amino Acid Tyr54 (H-donor) with distance 3.20 Å and energy of -1.98 K cal/mol.

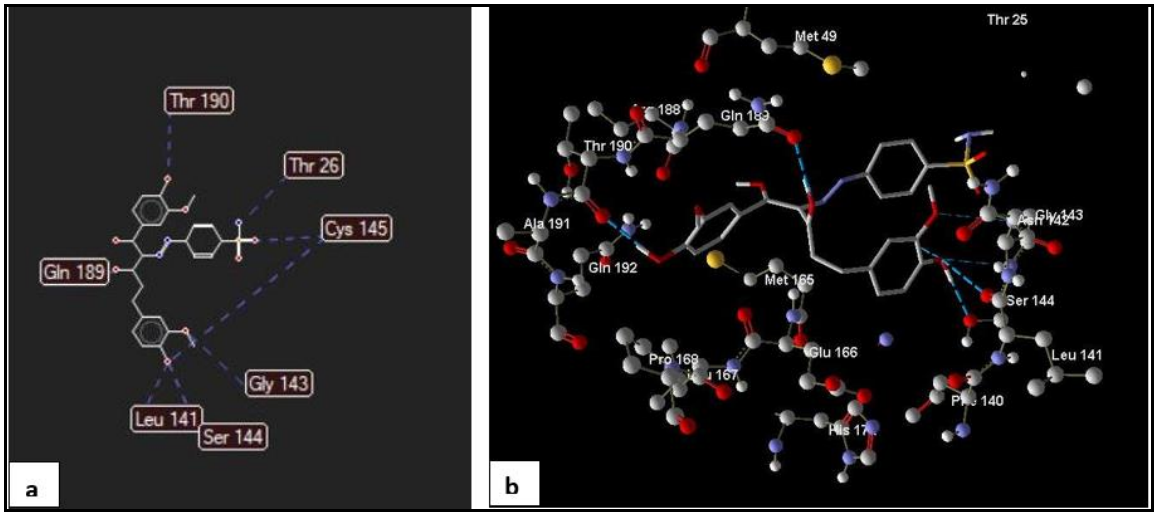

Fig. 16: 2D (a) and 3D (b) diagrams: interaction between curcumin derivative 13 and (6LU7). Amino Acid Ser144 (H-donor) with distance 3.07 Å and energy of -2.5 K cal/mol. Amino Acid Ser144 (H-acceptor) with distance 3.11 Å and energy of -1.01 K cal/mol. Amino Acid Leu141 (H-donor) with distance 3.08 Å and energy of -2.5 K cal/mol. Amino Acid Asn142 (H-donor) with distance 2.6Å and energy of -2.48 K cal/mol. Amino Acid Asp187 (H-donor) with distance 2.87Å and energy of -2.37 K cal/mol. Amino Acid Tyr54 (H-donor) with distance 2.62 Å and energy of -2.5 K cal/mol. Amino Acid Cys145(H-donor) with distance 3.26 Å and energy of -1.70 K cal/mol. Amino Acid Gly143(H-donor) with distance 3.44 Å and energy of -0.82 K cal/mol. Amino Acid Thr190 (H-donor) with distance 2.98 Å and energy of -2.5 K cal/mol. Amino Acid Thr26 (H-donor) with distance 2.85 Å and energy of -2.5 K cal/mol.

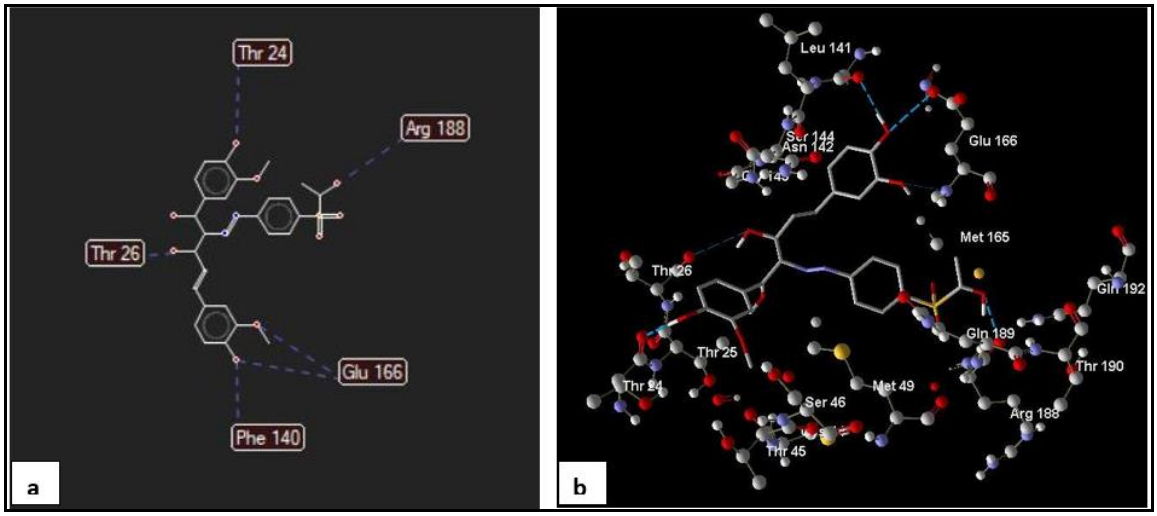

Fig.17: 2D (a) and 3D (b) diagrams: interaction between curcumin derivative 14 and (6LU7).Amino Acid Thr26 (donor rotatable) with distance 3.45 Å and energy of -0.76 K cal/mol. Amino Acid Thr24 (donor rotatable) with distance 2.72 Å and energy of -2.5 K cal/mol. Amino Acid Arg188 (donor rotatable) with distance 2.64 Å and energy of -2.5 K cal/mol. Amino Acid Glu166 (donor rotatable) with distance 3.12 Å and energy of -2.38 K cal/mol. Amino Acid Phe140 (donor rotatable) with distance 3.19 Å and energy of -2.50 K cal/mol.

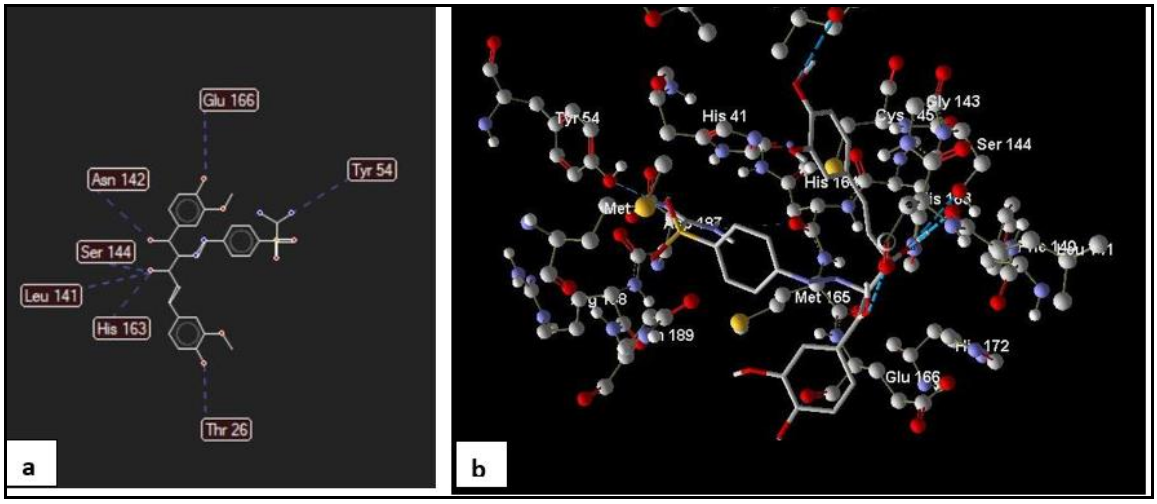

Fig. 18: 2D (a) and 3D (b) diagrams: interaction between curcumin derivative 15 and (6LU7). Amino Thr26 (donor rotatable) with distance 2.98 Å and energy of -2.50 K cal/mol. Amino Acid His163 (donor rotatable) with distance 3.02 Å and energy of -2.5 K cal/mol. Amino Acid Leu141 (donor rotatable) with distance 3.07, - 2.5 K cal/mol. Amino Acid Ser144 (donor rotatable) with distance 3.10 Å and energy of -3.1 K cal/mol. Amino Acid Asn142 (donor rotatable) with distance 3.00 Å and energy of -2.5 K cal/mol. Amino Acid Glu166 (donor rotatable) with distance 3.46 Å and energy of -0.69 K cal/mol. Amino Acid Tyr54 (donor rotatable) with distance 2.59 Å and energy of -1.21 K cal/mol.

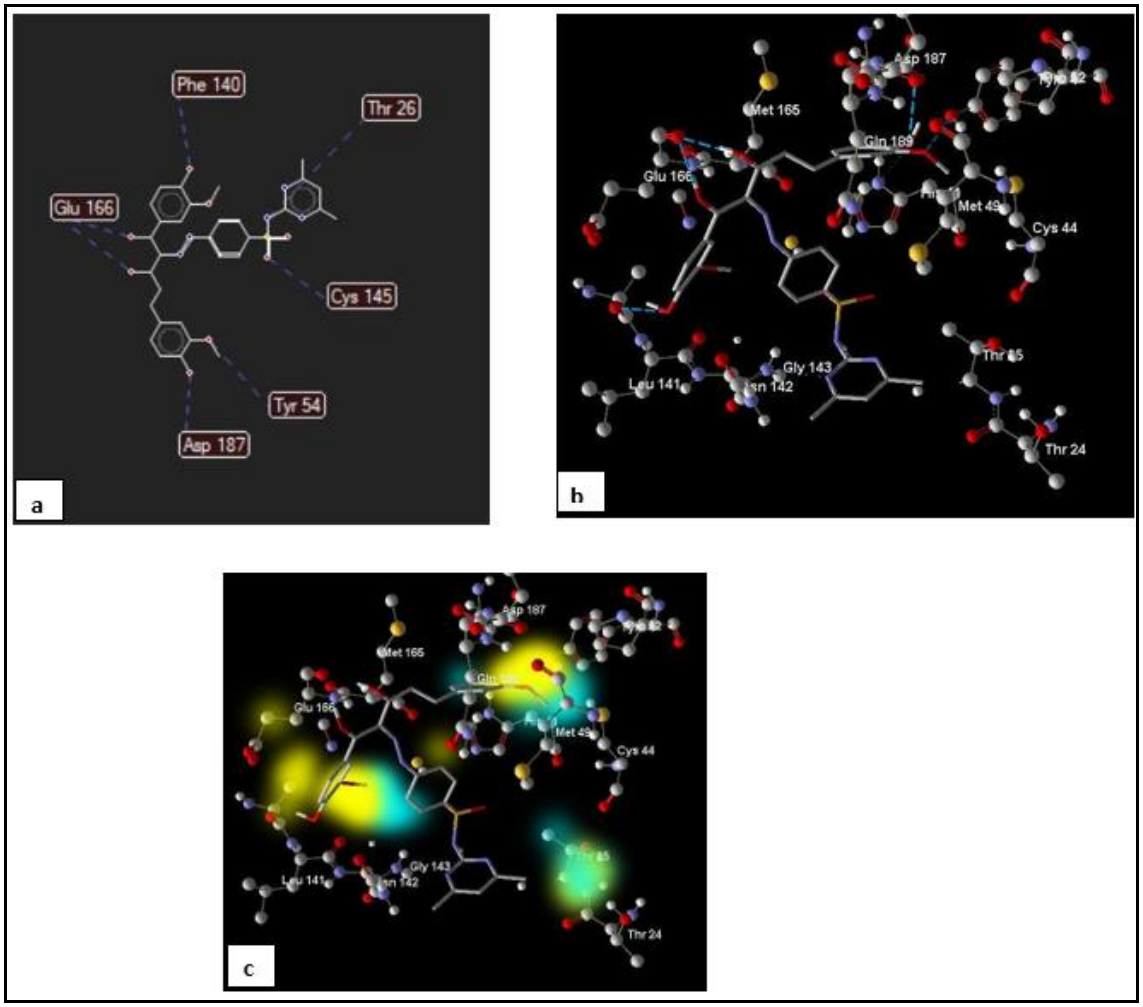

Fig. 19: 2D (a) and 3D (b) diagrams: interaction between curcumin derivative 16 and (6LU7). Amino Acid Glu166 (donor rotatable) with distance 2.93 Å and energy of -2.50 K cal/mol. Amino Acid Glu166 (donor rotatable) with distance 3.14 Å and energy of -2.29 K cal/mol. Amino Acid Phe140 (donor rotatable) with distance 2.74 Å and energy of -2.12 K cal/mol. Amino Acid Thr26 (H-acceptor) with distance 3.35 Å and energy of -1.23 K cal/mol. Amino Acid Cys145 (donor rotatable) with distance 2.72 Å and energy of -2.5 K cal/mol. Amino Acid Tyr54 (donor rotatable) with distance 3.14 Å and energy of -2.32 K cal/mol. Amino Acid Asp187 (donor rotatable) with distance 3.09 Å and energy of -2.50 K cal/mol. Blue color is hydrogen acceptor and yellow color is hydrogen donor (c).

DISCUSSION

To date, there is no specific antiviral treatment or vaccine for SARS-CoV-2, and the clinical management of COVID-19 is limited. Thus, safe and stable COVID-19 vaccines and drugs are needed to be developed (Wang et al., 2020). Most of the coronaviridae genome encodes two polyproteins, pp1a and, through ribosomal frameshifting during translation, pp1ab. These polyproteins are cleaved and transformed in mature non-structural proteins (NSPs) by the two proteases $3CL^{pro}$ (3C-like protease) and PL^{pro} (Papain Like Protease) encoded by the open reading frame 1. NSPs, in turn, play a principal role in the transcription/replication during the infection. Targeting these proteases may hence constitute a valid approach for antiviral drug design (Macchiagodena et al., 2020). Thus, we used the structure of

$3CL^{pro}$ from SARS-CoV-2(PDB code 6LU7) for molecular docking. Molecular docking is a widely employed method in structure-based drug design. The ligands used in this study are shown in figure (1) and for the first time the curcumin derivatives are shown in figure (2) (Gouda and Hussein, 2017). The active sites of SARS-CoV-2 6LU7 protein exist within the key amino acids; THR24, THR26, HIS41, THR45, MET 49, PHE140, LUE141, ASN142, GLY143, CYS145, HIS163, HIS164, MET165, GLU166, LEU167, PRO168, HIS172, ASP187, ARG188, GLN189, THR190, ALA191 (Figure 3) (Agrawal et al., 2020, Macchiagodena et al., 2020 and Khaerunnisa et al., 2020). Docking analysis showed that the H-bonds that interact with 6LU7 amino acids in the COVID-19 $3CL^{pro}$ active site. The binding energy results are related to the number of H-bonds formed with the active site pocket of COVID-19 $3CL^{pro}$. During this study, ligands have been docked into the active site of 6LU7 by using the Molgro Virtual Docker (MVD) software. Docking methods typically use an energy-based scoring function to identify the most energetically favorable conformation of a ligand when bound to the macromolecular target. Lower energy scores indicate more favored protein-ligand complexes. Molecular docking is thus an optimization problem, where the task is to find the ligand binding mode with the lowest potential energy. The process of docking involves sampling the coordinate space of the target binding site and scoring each possible ligand pose within that site, the highest-scoring pose then taken as the predicted binding mode for that compound (Naeem *et al.,* 2013).

The MolDock scores for drugs used for comparison purposes recorded in descending order were -65.4, -116.17, -123.62, -164.81 for favpiravir (avigan), hydroxychloroquine, chloroquine, and remdesivir respectively. For turmeric compounds and curcuminoids were -79.47, -95.28, -96.83, -102.42, -149.34, -151.45, -158.2 for alfa-curcumin, turmerone, alfa-zingiberene, alfa-tumerone, bisdemethoxcurcumin, demethoxycurcumin, and curcumin respectively. For semi-synthetic curcumin compounds were -167.41, -176.80, -181.71, -195.33, -197.64 for curcumin derivative 15, curcumin derivatives 14, 12, 16, and 13 respectively (Table 2). The lower MolDock score indicates that the drug-receptor interaction is more stable and could be used to predict the biological activity of the drug (Meizarini et al., 2018). Therefore, the lowest MolDock showed in the case of derivatives of curcumin followed by curcuminoids namely bisdemethoxcurcumin, demethoxycurcumin, and curcumin. Curcumin derivatives showed significant antioxidant activity (Gouda and Hussein, 2017). All the later eight compounds were shown to have a clear inhibitory effect against cyclooxygenase-2 revealing their possible use as new anti-inflammatory agents (Data not shown). Collectively, curcuminoids showed to have potential to be used as a therapy for many chronic diseases including cancer, cardiovascular, inflammatory, metabolic, neurological, lung and skin diseases, and various infectious diseases. The prominent safety and efficacy are some of the added advantages exhibited by these compounds. Noteworthy, the activity of curcumin in inhibiting many cytokines, suggests that it may be useful in the treatment of patients with the viral disease and cytokine storm (Kunnumakkara *et al.,* 2017). It inhibits the host inflammatory response potentially through their effects on cytokine/chemokine expression through the NFkB pathway (Avasarala *et al.,* 2013).

CONCLUSION

Studies of docking described herein deliver estimates of the inhibitory activities of the docked ligands. The results show that our ligands fit well in the active site of 6LU7 and also interact with

the residues in the active site which are important for their biological activity, thus, the studied ligands, more specifically the curcuminoids in addition to semi-synthetic curcumin compounds could be powerful inhibitors of Corona virus (SARS-CoV-2) protease and can be used to treat patients with that infection after further examinations *in vitro* and *in vivo*.

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REFERENCES

Aggarwal, B. B.; Surh, Y. J. and Shishodia, S. (eds). (2007). The molecular targets and therapeutic uses of curcumin in health and disease, 2007, Springer Science + Business Media, LLC.

Agrawal, A.; Jain, N. K.; Kumar, N. and Kulkarni, G. T. (2020). molecular docking study to identify potential inhibitor of COVID-19 main protease enzyme: an in-silico approach. ChemRxiv. Cambridge: Cambridge Open Engage; 2020; This content is a preprint and has not been peer-reviewed.

Avasarala, S.; Zhang, F.; Liu, G.; Wang, R.; London, S. D. and London, L. (2013). Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. *PLoS ONE;* 8(2) e57285.https://doi:10.1371/journal.pone.0057285

Gouda, M. A. and Hussein, B. H. M. (2017). Synthesis and anti-oxidant evaluation of some novel sulfa drugs. *Letters in Drug Design & Discovery*, 14; 1425-1432.https://www.rcsb.org/strcture/6LU7. Last accessed on 5/5/2020.

Khaerunnisa, S.; Kurniawan, H.; Awaluddin, R.; Suhartati, S.; Soetjipto, S. (2020). Potential Inhibitor of COVID-19 Main Protease (M^{pro}) From Several Medicinal Plant Compounds by Molecular Docking Study. *Preprints* 2020, 2020030226 (https://doi:10.20944/preprints202003.0226.v1). Khaerun

Kunnumakkara, A. B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N. K.; Prasad, S. and Aggarwal, B. B. (2017). Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases (Review article). *British Journal of Pharmacology*, 174; 1325–1348 https://doi:10.1111/bph.13621

Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K. S. M.; Lau, E. H. Y.; Wong, J. Y.; Xing, X.; Xiang, N.; Wu, Y.; Li, C.; Chen, Q.; Li, D.; Liu, T.; Zhao, J.; Liu, M.; Tu, W.; Chen, C.; Jin, L.; Yang, R.; Wang, Q.; Zhou, S.; Wang, R.; Liu, H.; Luo, Y.; Liu, Y.; Shao, G.; Li, H.; Tao, Z.; Yang, Y.; Deng, Z.; Liu, B.; Ma, Z.; Zhang, Y.; Shi, G.; Lam, T. T. Y.; Wu, J. T.; Gao, G. F.; Cowling, B. J.; Yang, B.; Leung, G. M.; Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *The New England Journal of Medicine*, 382(13): 1199-1207. https: //doi: 10.1056/NEJMoa2001316.

Macchiagodena, M.; Pagliai, M. and Procacci, P. (2020). Identification of potential binders of the main protease 3CLpro of the COVID-19 via structure-based ligand design and molecular modeling. *Chemical Physics Letters*, 137489. https://doi.org/10.1016/j.cplett.2020.137489

Meizarini, A.; Siswandono, R. W. and Rahayu, R. P. (2018). *In silico* and *in vivo* anti-inflammatory studies of curcuminoids, turmeric

extract with zinc oxide, and eugenol. *Tropical Journal of Pharmaceutical Research*, 17(2) 269-275. http://dx.doi.org/10.4314/tjpr.v17i2.11

Naeem, S.; Hylands, P. and Barlow, D. (2013). Docking studies of chlorogenic acid against aldose redutcase by using Molgro Virtual Docker software. *Journal of Applied Pharmaceutical Science*, 3(01) 013-020. https://doi.org/10.7324/JAPS.2013.30104

Praditya, D.; Kirchhoff, L.; Brüning, J.; Rachmawati, H.; Steinmann, J. and Steinmann, E. (2019). Anti-infective properties of the golden spice curcumin (Review). *Frontiers in Microbiology*, 10:912.https://doi.org/10.3389/fmicb.2019.00912

Shahidi, F. and Hossain, A. (2018). Bioactives in spices, and spice oleoresins: Phytochemicals and their beneficial effects in food preservation and health promotion. *Journal of Food Bioactives*, 3: 8–75.

Sordillo, P. P. and Helson, L. (2015). Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections (Review). *in vivo*, 29: 1-4.

Venkatesan, N.; Punithavathi, D. and Babu, M. (2007). Protection from acute and chronic lung diseases by curcumin. In: Aggarwal BB, Surh Y-J, and Shishodia S (eds). The molecular targets and therapeutic uses of curcumin in healthanddisease, pp379-504, Springer Science+ Business Media, LLC.

Wang, L.; Wang, Y.; Ye, D. and Liu, Q. (2020). Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. *International Journal of Antimicrobial Agents*, Jun; 55(6) 105948. https://doi.org/10.1016/j.ijantimicag.2020.105948

Wu, F.; Zhao, S.; Yu, B.; Chen, YM.; Wang, W.; Song, Z. G.; Hu, Y.; Tao, Z. W.; Tian, J. H.; Pei, Y. Y.; Yuan, M. L.; Zhang, Y. L.; Dai, F. H.; Liu, Y.; Wang, Q. M.; Zheng, J. J.; Xu, L.; Holmes, E. C. and Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, 579(7798) 265-269.https://doi.org/10.1038/s41586-020-2008-3.

Zhou, P.; Yang, X. L.; Wang, X. G.; Hu, B.; Zhang, L.; Zhang W.; Si, H. R.; Zhu, Y.; Li, B.; Huang, C. L.; Chen, H. D.; Chen, J.; Luo, Y.; Guo, H.; Jiang, R. D.; Liu, M. Q.; Chen, Y.; Shen, X. R.; Wang, X.; Zheng, X. S.; Zhao, K.; Chen, Q. J.; Deng, F.; Liu, L. L.; Yan, B.; Zhan, F. X.; Wang, Y. Y.; Xiao, G. F. and Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798) 270-273. https://doi.org/10.1038/s41586-020-2012-7.

Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; Niu, P.; Zhan, F.; Ma, X.; Wang, D.; Xu, W.; Wu, G.; Gao, G. F. and Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *The New England Journal of Medicine*, 382(8) 727-733. https://doi.org/10.1056/NEJMoa2001017.

ARABIC SUMMARY

التأثير الضد فيروسي المتوقع للكوركومين ومشتقاته ضد فيروس كورونا المستجد باستخدام نهج الإرساء الجزيئي

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يعد فيروس كورونا المستجد وباءً حديثًا ينتشر في جميع أنحاء العالم مسببا الملايين من حالات العدوى والوفيات. ولا توجد حاليًا علاجات ناجعة لعلاج العدوى بفيروس كورونا. وفي المجتمع العلمي تم توجيه العديد من الدراسات لفحص ودراسة العديد من تراكيب الفيروس لتكون أهدافا حيوية للأدوية، وقد تم دراسة التراكيب ونتائج الفحص للمستهدفات الهامة مثل(3CL^{pro}) 3-chymotrypsin-like protease. أيضا من المعروف أن مستخلصات الكركمين والكركم قد أظهرت نشاطًا بارزًا كمضادات للالتهابات، والفيروسات، والبكتيريا، والفطريات، علاوة على أنها أظهرت تأثيرًا إيجابيًا على عاصفة السيتوكينات في العديد من الدراسات السابقة. في هذه الدراسة، وباستخدام طريقة الإرساء الجزيئي (molecular docking)، أمكننا تحديد مثبطات جديدة محتملة لـفيروس كورونا باستخدام الكوركومينويدات (Curcuminoids)ومشتقات الكركمين. ويوفر اكتشاف تركيب M^{pro} protease في تركيب فيروس كورونا المستجد فرصة رائعة لتحديد الأدوية المحتملة للعلاج. وقد تم التركيز على proteases الرئيسية في فيروس كورونا ومدى ارتباطها بالمركبات والأدوية محل الدراسة، وذلك بغرض المقارنة، باستخدام Molegro. وقد نتج عن التحام الكركومينويدات ومشتقات الكركمين في الموقع النشط 6UL7 درجات طاقة أقل مما يشير إلى تكوين تراكيب أكثر ترابطا للبروتين مع المركبات المفحوصة. هذا وقد أظهرت الكركومينويدات وخمسة مشتقات من الكركمين أن لديها أفضل قدرة للعمل كعلاجات ممكنة لفيروس كورونا المستجد. وهذه النتائج من الممكن أن تكون إضافة جديدة جيدة في دراسات مستقبلية لاستكشاف الاستخدام الطبي للمركبات المفحوصة كمضادات للعدوى بفيروس كورونا.