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Applying computer simulations in battling with COVID-19, *using pre-analyzed molecular and chemical data to face the pandemic*

Mohammad Amin Khazeei Tabari [a,b,1], Hooman Khoshhal [a,b,1], Alireza Tafazoli [c,d], Mohanna Khandan [a,b], Abouzar Bagheri [e,*]

[a] *Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran*
[b] *USERN Office, Mazandaran University of Medical Sciences, Sari, Iran*
[c] *Department of Analysis and Bioanalysis of Medicines, Faculty of Pharmacy with the Division of Laboratory Medicine, Medical University of Białystok, Białystok, Poland*
[d] *Genomics Laboratory, Clinical Research Centre, Medical University of Białystok, Bialystok, Poland*
[e] *Department of Clinical Biochemistry and Medical Genetics, Faculty of Medicine, Molecular and Cell Biology Research Center, Mazandaran University of Medical Sciences, Sari, Iran*

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has made many concerns for healthcare services especially, in finding useful therapeutic(s). Despite the scientists' struggle to find and/or creating possible drugs, so far there is no treatment with high efficiency for the disease. During the pandemic, researchers have performed some molecular analyses to find potential therapeutics out of both the natural and synthetic available medicines. Computer simulations and related data have shown a significant role in drug discovery and development before. In this field, antiviral drugs, phytochemicals, anti-inflammatory agents, etc. were essential groups of compounds tested against COVID-19, using molecular modeling, molecular dynamics (MD), and docking tools. The results indicate promising effects of such compounds to be used in further experimental and clinical trials; Chloroquine, Chloroquine-OH, and Umifenovir as viral entry inhibitors, Remdesivir, Ribavirin, Lopinavir, Ritonavir, and Darunavir as viral replication inhibitors, and Sirolimus are the examples, which were tested clinically on patients after comprehensive assessments of the available data on molecular simulation. This review summarizes the outcomes of various computer simulations data in the battle against COVID-19.

1. Introduction

Coronaviruses (CoVs) are major respiratory disease pathogens. They are single-stranded RNA viruses (+ssRNA) and could be found in various animal species [1]. CoVs transmit from other species to humans and cause mild to severe types of disorders [2]. Recently a kind of CoV family, called SARS-CoV-2, has become pandemic worldwide, made a global concern for all societies [3]. It is the third pathogenic and transmittable virus after previous outbreaks for this family, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Finding any effective treatment to prevent an epidemic/pandemic difficulty is necessary for such situations [4]. COVID-19 is a disorder caused by SARS-CoV-2, which has been recently named by WHO [5]; More knowledge on its structural characteristics and general features can help scientists to defeat this outbreak. Based on the SARS-CoV-2 molecular structure, computer simulations data utilization for drug prediction and development could be conducted through comprehensive databases to find promising medications for this type of CoV [6]. The current review will categorize the data for specific compounds, found by computer simulations against COVID-19, and try to raise the knowledge about possible therapy for this novel disease.

2. Comparing genomic and structural characterization of SARS-CoV-2 to other CoVs, based on available *in-silico* data

SARS-CoV-2 is a single-stranded RNA with 29891 nucleotides, which encodes 9860 amino acids [7]. The nucleotide sequence shows 82% similarity to other coronaviruses. The SARS-CoV-2 genome organization

* Corresponding author. Department of Clinical Biochemistry and Medical Genetics, Faculty of Medicine, Molecular and Cell Biology Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
E-mail address: a.bagheri@mazums.ac.ir (A. Bagheri).
[1] These authors contributed equally in preparation of the manuscript.

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is arranged as following: 5′-replicase (ORF1/ab) -structural proteins [Spike (S) -Envelope (E) -Membrane (M) -Nucleocapsid (N)]−3′, without the hemagglutinin-esterase gene, which introduced as a common gene found in lineage Aβ- CoVs [8]. A comprehensive study on the amino acid sequence of the viral nucleocapsid proved bat coronavirus RaTG13 has the most similar nucleocapsid (>99%) with the one in SARS-CoV-2 [9]. The virus has 12 recognized open reading frames (ORFs) expressed by nine mRNAs. SARS-CoV-2 genome sequencing demonstrated that ORF1a/b is closely similar to those from the bat, civet, and other human SARS- CoVs, but the external sub-domain amino acid sequence of the spike receptor-binding domain for this novel virus is only 40% similar to other SARS-related coronaviruses. SARS-CoV-2's new ORF8 encodes a secretory protein with an alpha-helix, following a six-strand beta-sheet. It was also shown that ORF3b encodes a new short protein comparing to other CoVs. The 5′-and 3′-UTR sequences are identical to other β-CoVs in more than 83.5% [8].

To find the origin of SARS-CoV-2, two separate cDNA pools were utilized for genomic sequence comparison; one from the *Carassius auratus* cell line and the other one from *Ctenopharyngodon idella* head kidney tissue. Translated nucleotide BLAST (TBLASTN) analysis revealed two cDNA clones (one from each pool) were remarkably similar to SARS-like-coronaviruses. The first clone included 152 amino acids that covered 2% of the SARS-CoV-2 genome and was 93.42% equal. The second also encompassed an 88 amino acid sequence, which covered 1% of the SARS-CoV-2 genome with 93.18% equality. Therefore SARS-like-coronaviruses are general environmental pathogens that may even originate from lentic regions [10].

2.1. Non-structural proteins

The virus has 16 recognized non-structural proteins (NSPs), including two viral cysteine proteases called NSP-3 (papain-like protease) and NSP-5 (chymotrypsin-like, 3C-like, or main protease), NSP-13 (helicase), NSP-12 (RNA-dependent RNA polymerase [RdRp]), and other NSPs that play a role in viral replication and translation procedures [8].

2.2. Structural proteins

CoV spike protein is a Class I fusion protein of CoVs [11], which are considered as an essential factor in host cell recognition [12]. The spike protein contains S1–S2 heterodimers that bind to angiotensin-converting enzyme 2 (ACE2) in the human body [13]. Molecular docking studies demonstrated residues near lysine 31 and tyrosine 41, 82–84, and 353_357 in the human ACE2 have a significant binding site for spike protein in SARS-CoV [14,15]. It has an essential part in viral cell entry via ACE2 receptors [16] and could be defined as a suitable target for therapeutic agents [13]. The virus S1 protein consists of a signal peptide, an N-terminal domain, and a receptor-binding domain. In contrast, S2 protein comprises conserved fusion peptide (FP), heptad-repeat 1 and 2, transmembrane, and cytoplasmic domains. S1 and S2 subunits demonstrate 70 and 99% similarity with two bat SARS-like CoVs (SL-CoVZXC21 and ZC45) and other human SARS-CoVs [8].

Also, the binding energy of the SARS-CoV-2 spike protein to ACE2 (−15.7 kcal/mol) is higher than SARS-CoV (−14.1 kcal/mol). Therefore, SARS-CoV-2 can make more protein-protein contact and interactions. This has helped this virus to be hard to control and rapid spread in humans [17].

Based on parallel bioinformatics predictions, it has been demonstrated that some amino acid sequences of SARS-CoV-2 may act as B or T-cell epitopes, and this can help scientists for designing potential vaccines. Also, five regions in SARS-CoV spike glycoproteins (residues 274–306, 510–586, 587–628, 784–803, and 870–893) showed a significant immune response. The three were part of the S1 subunit in the C-terminal domain (CTD) 2 and 3, and the other two were in the HR1 domain of the S2 subunit [18].

Virus envelop protein (E-protein) plays a role in each function of assembly, budding, envelope formation, and pathogenesis [19]. This protein in SARS-CoV-2 has a 94.74% structure similarity to previous SARS-CoV E-proteins. Each unit of SARS-CoV-2 E-protein contains seven alpha-helices and eight loops. According to the complete structure data, which includes five homo-units, the whole configuration consists of 35 alpha-helices and 40 loops. As a result, this protein can be a possible target to inhibit SARS-CoV-2 cellular function, too [20]. According to genome sequencing data, SARS-CoV E-protein is similar to the sequences from Pangolin CoV MP798 and Bat CoV CoVZXC21, CoVZC45, and RaTG13 isolates [21].

The CoV membrane protein (M) is a transmembrane protein used for virus assembly in endoplasmic-reticulum and Golgi complex [22]. The M protein has 221–230 residues and is the most abundant viral envelope protein. The M protein is significantly hydrophobic with three domains [23]. Sequence alignment shows a significant (98%) between SARS-CoV-2 and the sequences from Bat and Pangolin isolates [21].

Studies reported 3-chymotrypsin-like cysteine protease (3CLpro) is an essential viral structure that takes part in viral replication and life cycle [24]. SARS-CoV-2 3CLpro is 99.02% similar to bat SARS-like coronaviruses. The existence of structural data on this protein in SARS-CoV-2 can also bring insight for drug targeting to stop viral replication and life cycle [25].

Moreover, SARS-CoV, WIV1–CoV, and SARS-CoV-2 RNA receptor binding domains (RBDs) were compared, and the results showed the root mean square deviation (RMSD) of atomic positions value of binding of these RBDs to ACE2 were 1.2 for SARS-CoV and 0.9 for WIV1–CoV and SARS-CoV-2. This measurement of the average distance between the atoms approved that SARS-CoV-2 is more similar to WIV1–CoV than SARS-CoV. However, it also has three mutations in its RBD comparing to WIV1–CoV [26].

3. Computer simulations and molecular docking and molecular dynamics data for COVID-19

3.1. Antiviral protease activity

Throughout screening from previously published studies on natural compounds with potential antiviral activity and investigating their activity against the SARS-CoV-2 3CLpro homology model, researchers found some natural molecules that can be used against COVID-19. The analyses showed nine non-toxic compounds with an ability to be formulated as drugs and effectively bound with the receptor binding site and catalytic dyad (Cys-145 and His-41) of SARS-CoV-2 3CLpro including, 5,7,3′,4′-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone from *Psorothamnus arborescens* (−29.57 kcal/mol), Myricitrin from *Myrica cerifera* (−22.13 kcal/mol), Methyl rosmarinate from *Hyptis atrorubens Poit* (−20.62 kcal/mol), 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-O-beta-D-glucopyranoside from *Phaseolus vulgaris* (−19.10 kcal/mol), (2S)-Eriodictyol 7-O-(6″-O-galloyl)-beta-D-glucopyranoside from *Phyllanthus emblica* (−19.47 kcal/mol), Calceolarioside B from *Fraxinus sieboldiana* (−19.87 kcal/mol), Myricetin 3-O-beta-D-glucopyranoside from *Camellia sinensis* (−18.42 kcal/mol), Licoleafol from *Glycyrrhiza uralensis* (−19.64 kcal/mol) and Amaranthin from *Amaranthus tricolor* (−18.14 kcal/mol). The binding affinity of these chemicals was further compared to Nelfinavir, Prulifloxacin, and Colistin, which were previously predicted as effective drugs in COVID-19 [27]. 5,7,3′,4′-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone had been used as an anti-leishmanial agent in previous studies [28]. The results show that this isoflavone with the highest binding affinity among others (−29.57 kcal/mol) and might be the most effective compound against SARS-CoV-2 3CLpro.

Molecular dynamics (MD) simulations were used to investigate docking results and determine the binding behavior and stability of potential compounds. 5,7,30,40-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, myricitrin, and methyl rosmarinate were undergone MD

simulation for 50 ns. RMSD shows the stability of ligand-protein complexes. All three were stable, with RMSD values of 1.6 ± 0.02 Å,1.5 ± 0.02 Å, and 1.7 ± 0.02 Å for 5,7,30,40-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, myricitrin, and methyl rosmarinate, respectively. The main catalytic dyad residues (Cys-145 and His-41) demonstrated stable behavior. Radius of gyration (ROG) shows protein compactness, stability, and folding, and all three compounds showed normal behavior in the 50 ns simulations. An investigation on hydrogen bonds revealed that the SARS-CoV-2 3CLpro internal hydrogen bonds stay stable through the simulation. All the data show that these three phytochemicals might be useful in COVID-19 treatment [27].

Thirteen compounds including Betulinic acid, Coumaroyltyramine, Cryptotanshinone, Desmethoxyreserpine, Dihomo-γ-linolenic acid, Dihydrotanshinone I, Kaempferol, Lignan, Moupinamide, N-cis-feruloyltyramine, Quercetin, Sugiol, and Tanshinone IIa were tested against viral proteases including PLpro and 3CLpro and viral spike protein using docking data. These chemicals bind to the thumb and palm domains of 3CLpro and interfere with the entry of substrates into active sites of this enzyme [29]. Furthermore, searching on the TCMSP database [30] resulted in 26 herbal entities within 11 types of plants, including *Forsythiae fructus*, *Licorice, Mori cortex, Chrysanthemi flos, Farfarae flos, Lonicerae japonicae flos, Mori follum, Peucedani radix, Rhizoma fagopyri cymosi, Tamaricis cacumen, Erigeron breviscapus, Radix bupleuri, Coptidis rhizoma, Houttuyniae herba, Hoveniae dulcis semen, Inulae flos, Eriobotryae folium, Hedysarum multijugum maxim, Lepidii semen descurainiae semen, Ardisiae japonicae herba, Asteris radix et rhizoma, Euphorbiae helioscopiae herba, Ginkgo semen, Anemarrhenae rhizoma, Epimrdii herba*, and *Fortunes bossfern rhizome*, which contain 13 mentioned components above. The plants proved to be effective in treating respiratory infections, immune/inflammatory reaction, and hypoxia. The docking study showed that Cryptotanshinone had the highest binding affinity to PLpro (−5.25 kcal/mol), Quercetin had the highest binding affinity to 3CLpro (−6.25 kcal/mol), and Dihydrotanshinone I had the highest binding affinity to viral spike protein (−5.16 kcal/mol) [29].

Previous studies show that HIV-1 protease inhibitors can also block SARS-CoV protease [31]. The effects of HIV-1 protease inhibitors, including Saquinavir, Lopinavir, Tipranavir, Darunavir, Amprenavir, Atazanavir, and Ritonavir on the SARS-CoV-2 main protease were analyzed by docking models. Data analysis showed that these compounds have the potential to bind to the active site of SARS-CoV-2 protease. Their binding energies were −9.6 kcal/mol for Saquinavir, −9.1 kcal/mol for Lopinavir, −8.7 kcal/mol for Tipranavir, −8.2 kcal/mol for Darunavir, −7.6 kcal/mol for Amprenavir, −7.2 kcal/mol for Atazanavir, and −6.9 kcal/mol for Ritonavir. The component with the most potent interaction with the SARS-CoV-2 main protease active site was Saquinavir (−9.6 kcal/mol) according to its binding energy. On the other side, digging in PubChem and ZINC for protease inhibitors resulted in finding 20 chemicals. These chemicals were chosen for investigations based on their binding energy with viral protease. Five elements classified by the following IDs: 444603 (−8.7 kcal/mol), 444743 (−8.3 kcal/mol) and 444745 (−9.3 kcal/mol), ZINC0010114061081 (−8.7 kcal/mol), ZINC001014061061 (−7.8 kcal/mol) were the best compounds that had the highest binding energy to SARS-CoV-2 main protease [32].

Other researchers utilized Vina calculation assays to find the best chemicals in the field. The Vina scoring were compared among thirteen protease inhibitors against HIV including Saquinavir (−9.3 kcal/mol), Indinavir (−8.7 kcal/mol), Tipranavir (−8.6 kcal/mol), Ritonavir (−8.1 kcal/mol), Lopinavir (−8.1 kcal/mol), Atazanavir (−8.0 kcal/mol), Nelfinavir (−7.9 kcal/mol), Amprenavir (−7.7 kcal/mol), Darunavir (−7.6 kcal/mol) and Fosamprenavir (−7.2 kcal/mol) and against HCV including Simeprevir (−10.0 kcal/mol), Faldaprevir (−8.4 kcal/mol), Asunaprevir (−8.1 kcal/mol) were introduced as the best compounds binding to 3CLpro [33]. Surprisingly Simeprevir, an HCV NS3/4A protease inhibitor [34], showed a higher binding energy than other best-known inhibitors of SARS–CoV-2 proteases, such as Lopinavir (−8.1 kcal/mol) [35] and Nelfinavir (−7.9 kcal/mol) [36]. Protease drug discoveries are mainly driven by hydrophobic interactions, and docking investigations show how these molecules fill the hydrophobic pockets that flank the catalytic dyad [37,38].

3.2. Antiviral RdRp

Theaflavin has shown the potential to act as an anti-SARS-CoV-2 RdRp. Inhibitory effects of Theaflavin were compared between SARS-CoV-2, SARS-CoV, and MERS CoV RdRp using docking [25]. Idock scores [39] demonstrated that Theaflavin had a higher binding energy to SARS-CoV-2 (−9.11 kcal/mol) than SARS-CoV (−8.03 kcal/mol), and MERS-CoV (−8.26 kcal/mol) in the catalytic pocket of RdRp [25]. The study was completed using Achilles blind docking server [40] and the results showed lower binding energy (−8.8 kcal/mol) when Theaflavin docks in the catalytic pocket of SARS-CoV-2. The binding interaction happens between Theaflavin and Asp452, Arg553 and Arg624 of SARS-CoV-2 RdRp [25].

In another study three types of RdRps (SARS-CoV-2 RdRp, SARS RdRp, and HCV RdRp) were targeted with four physiological nucleotides (GTP, UTP, CTP, and ATP), five approved drugs against various viral RdRps (Galidesivir, Remdesivir, Tenofovir, Sofosbuvir, and Ribavirin), 13 chemicals that have been used against HCV NS5B RdRp (Uprifosbuvir, Setrobuvir, Balapravir, MK0608, R7128 IDX-184, 2′ C-methylcytidine, BMS-986094, YAK, PSI-6130, PSI-6206, R1479, and Valopectibine) plus two other negative control compounds with no affinity to RdRp (Cinnamaldehyde and Thymoquinone). According to observations on RdRps active site, the region surrounding the D255 and D256 residues is the most accessible surface in all Human CoVs (HCoVs). Data also stated that two phosphate nucleotides (ATP and GTP), five drugs (Galidesivir, Remdesivir, Tenofovir, Sofosbuvir, and Ribavirin) in addition to Setrobuvir, IDX-184, and YAK have appropriate binding energy to SARS-COV-2 RdRp, which were −7,-8.7, −7.0, −7.6, −6.9, −7.5, −7.8 -9.3, −9.0, and −8.4 kcal/mol respectively. According to binding energy data, the best compounds with potential high affinity to SARS-CoV-2 RdRp were Setrobuvir (−9.3 kcal/mol), IDX-184 (−9.0 kcal/mol), and YAK (−8.4 kcal/mol). Setrobuvir and YAK formed H-bonds, hydrophobic contacts, (p)-cation contacts and halogen interactions with RdRp and IDX-184 showed the same interaction pattern as GTP (its parent nucleotide) in binding the RdRp [41].

Other analyzed data included anti-RdRp activity of eight anti-HCV drugs, including Sofosbuvir, IDX-184, Ribavirin, Remdisivir, Guanosine triphosphate (GTP), Uracil triphosphate (UTP), Cinnamaldehyde, and Thymoquinone were tested against SARS-CoV-2 RdRp; Investigations showed the drugs have stable binding energy to SARS-CoV RdRp; IDX-184 (−9 kcal/mol) and sofisbuvir (−7.5 kcal/mol) can potentially be better inhibitors for COVID-19 compared to other medications mentioned above as a result of their higher binding energy [42].

Eight anti-HCV drugs, including Sofosbuvir, IDX-184, Ribavirin, Remdisivir, Guanosine triphosphate (GTP), Uracil triphosphate (UTP), Cinnamaldehyde, and Thymoquinone were tested against SARS-CoV-2 RdRp through molecular docking. Results demonstrated that IDX-184 (−9 kcal/mol) and sofisbuvir (−7.5 kcal/mol) might be better compounds against COVID-19 according to their binding energy.

3.3. Antiviral E protein

E proteins are associated with viral pathogenesis in SARS-CoV-2. Belachinal (−11.46 kcal/mol), Macaflavanone E (−11.07 kcal/mol), Vibsanol B (−11.07 kcal/mol), 14 R*,15-Epoxyvibsanin C (−10.56 kcal/mol), Macaflavanone C (−10.49 kcal/mol), Luzonoid D (−10.47 kcal/mol), Grossamide K (−10.50 kcal/mol), (-)-Blestriarene C (−10.40 kcal/mol), Macaflavanone F (−10.36 kcal/mol) and Dolichosterone (−10.31 kcal/mol) were evaluated for antiviral E protein activity. Results from a docking study showed that Belachinal, Macaflavanone-E, and Vibsanol-

Table 1
Best predicted compounds for COVID-19 treatment using molecular docking methods.

Compound	Source	Target	Effect	Binding energy (kcal/mol)	Docking method	Ref
5,7,3′,4′-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	Natural	3CLpro	Cell cycle and replication will be arrested	−29.57	Molecular operating environment (MOE)	[27]
Dihydrotanshinone I	Natural	Spike protein	Inhibition of viral entry	−5.16	Autodock	[29]
Cryptotanshinone	Natural	PL^{pro}	Inhibition of SARS-CoV-2 cell cycle and replication	−5.25	Autodock 4	[29]
Quercetin	Natural	$3CL^{pro}$	Inhibition of SARS-CoV-2 cell cycle and replication	−6.25	Autodock 4	[29]
Theaflavin	Natural	RdRp	Inhibition of viral replication	−9.11[a] −8.8[b]	Idock and blind docking server	[25]
Belachinal, Macaflavanone-E Vibsanol-B	Natural	E protein	Inhibition of viral entry	−12.35 −11.96 −11.97	Autodock tool	[20]
IDX-184 Sofisbuvir	Synthetic	RdRp	Inhibition of viral replication	−9.0 −7.5	AutoDock Vinasoftware implemented in SCIGRESS	[42]
Setrobuvir IDX-184 YAK	Synthetic	RdRp	Inhibition of replication	−9.3 −9.0 −8.4	Autodock vina	[41]
Saquinavir	Synthetic	3CLpro	Inhibition of SARS-CoV-2 cell cycle and replication	−9.6	VINA/VegaZZ 3.1.0.21 and 30	[32]
444603 **444743** **444745** **ZINC0010114061081** **ZINC001014061061**	Synthetic	3CLpro	Inhibition of SARS-CoV-2 cell cycle and replication	−8.7 −8.3 −9.3 −8.7 −7.8	VINA/VegaZZ 3.1.0.21 and 30	[32]
Simeprevir	Synthetic	3CLpro	Inhibition of SARS-CoV-2 cell cycle and replication	−10.0	Autodock vina	[33]
Umifenovir **Pleconaril** **Enfuvirtide**	Synthetic	Spike protein	Inhibition of viral entry	−7.7 −7.1 −5.9	Autodock vina	[33]
CLQ CLQ-OH	Synthetic	Sialic acid of host cell ganglioside	Inhibition of virus attachment to host cell	−10.7553 −10.9943	Hyperchem and Molegro Molecular viewer	[43]

[a] In the catalytic pocket of RdRp in SARS-COV-2.
[b] Blind docking in the catalytic pocket of SARS-COV-2.

B (isolated from *Belamcanda chinensis*, *Macaranga tanarius,* and *Viburnum odoratissimum* respectively) caused a reduction in SARS-CoV-2 E-protein's functional activity with higher binding affinity than other compounds. Two amino acids, including VAL25 and PHE26, showed a strong interaction with these three phytochemicals. Belachinal, Macaflavanone E, and Vibsanol B have also passed the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity). Based on the results, these three phytochemicals might be considered as therapeutics against COVID-19 in further studies. Structural features of the SARS-CoV-2 E protein was performed via molecular dynamics analyzes in 200 ns. RMSD was stable subsequently 170 ns with a value of 2.74 Å. RMSF fluctuates an average value of 5.96 Å. Amino acids with maximum fluctuation within 200 ns were VAL17, ALA22, LEU19, LEU27, PHE23, PHE26, LEU27, VAL24, VAL25, VAL29, ILE33, ALA36, and TYR42 [20]. These residues may help as a biomarker in further drug discoveries [43].

3.4. Antiviral spike protein

N-terminal domain (NTD) of spike protein in virus binds to sialic acids linked to host cell surface gangliosides. Molecular dynamics simulations show that many amino acids are essential for the interaction between NTD of spike protein and sialic acid, especially Phe-135, Asn-137, and Arg-158. Chloroquine (CLQ) and Hydroxychloroquine (CLQ-OH) are two possible drugs for targeting sialic acid [44]. Coronaviruses interact with a specific sialic acid called 9-O-acetyl-N-acetylneuraminic (9-O-SIA) [45]. CLQ showed a significant energy −45 kJ/mol (−10.7553 kcal/mol) through interacting with sialic acid. The carboxylate group of the sialic acid of GM1 was oriented towards the cationic groups of CLQ. CLQ-OH had a little more stable connection with sialic acid because of making hydrogen bonds, and the energy was −46 kJ/mol (−10.9943 kcal/mol). As a result, binding CLQ and CLQ-OH inhibit SARS-CoV-2 entry to cells [44].

Umifenovir, Pleconaril, and Enfuvirtide binding affinity to spike protein were also compared by molecular docking and the binding energies were −7.7, −7.1, and −5.9 kcal/mol [33].

4. Network-based drug repurposing

A network-based drug repurposing method also was used to select possible therapeutics against COVID-19, which included selective Estrogen Receptor Modulators (SERM), Angiotensin Receptor Blockers (ARB), Immunosuppressant or Anti-Neoplastic Agents (ANA), and Anti-inflammatory agents. SERMs like toremifene affect HCoV host proteins including RPL19 (with a role in protein catalysis), HNRNPA1 (with a role in mRNA metabolism), NPM1 (that binds to the single-stranded and double-stranded nucleic acids), EIF3I (encodes a protein that interacts with TGFβ), EIF3F (interacts with mammalian target of rapamycin), and EIF3E (that has a role in viral mRNA translation) [46]. ARBs such as Irbesartan can inhibit Sodium/Bile Acid Co-Transporter Proteins (NTCP), which prevent viral entry too. Immunosuppressant and ANAs like mercaptopurine target host proteins in HCoVs such as JUN, PABPC1, NPM1, and NCL. Anti-inflammatory factors such as melatonin also affect HCoV cellular targets like ACE2, BCL2L1, JUN, and IKBKB in an indirect way. ACE2 enables virus entrance to the host cell [13], BCL2L1 has a role in cell apoptosis [47], JUN has a role in cellular proliferation and apoptosis [48] and IKBKB has a role in cytokine-activated cellular signaling pathway in immune responses [49]. Finally, Sirolimus is presented as a viral protein expression blocker [46]. Because of the following studies, a possible drug regimen was recommended.

1. Sirolimus plus Dactinomycin considered as an inhibitor for MTOR signaling and RNA synthesis pathway in HCoV-infected cells [50].

Table 2
Best predicted compounds for COVID-19 treatment using network based drug repurposing.

Compound	Source	Target and Effect	Ref
Sirolimus Dactinomycin	Synthetic	Inhibition of MTOR signaling and RNA synthesis pathway	[46]
Toremifene Emodin	Synthetic Natural	Depression of SARS-COV associated 3a protein Distraction of interaction between SARS-COV spike protein and ACE2	[47,48]
Mercaptopurine Melatonin	Synthetic	Inhibition of plain like protease, ACE2, c-JUN signaling and inducing anti-inflammatory pathways	[49–52]
Didanosine benzyl-quinazolin-4-yl-amine camptothecin RO-90-7501	Synthetic	Downregulation of *PNP* Downregulation of *EGFR* Downregulation of *TOP1* and *HIF1A* Downregulation of *APP*	

2. Toremifene and Emodin; the combination of Toremifene as a SERM and Emodin can decrease SARS-CoV associated 3a protein level in cells [51] and also distract interaction between SARS-CoV spike protein and ACE2 [52].
3. Mercaptopurine plus melatonin; in vitro and in vivo studies showed that these two drugs could be a therapeutic approach for COVID-19 by showing the effects on the plain like protease of the virus [53], ACE2 [54], c-JUN signaling [55], and anti-inflammatory pathways [56].

Other storage data also indicated to 30 differentiated expressed genes, including SLC1A5, CXADR, CAV2, NUP98, CTBP2, GSN, HSPA1B, STOM, and RAB1 as up-regulated ones in type II alveolar cells of affected patients. Strategies to down-regulating these genes could be helpful in treatment procedures, as the genes control viral transmission and replication [57]. Combined search of the Connectivity Map Linked User Environment (CLUE) platform and Library of Integrated Network-Based Cellular Signatures (LINCS) helped the researchers to find compounds that are going to down-regulate these genes [58]. Based on equations [59], four drugs of Didanosine, Benzyl-quinazolin-4-yl-amine, Camptothecin, and RO-90-7501 showed the highest score in this field. PNP, EGFR, TOP1, HIF1A, and APP were introduced as the target genes of these drugs [60]. In this regard, Didanosine is an anti-HIV drug of nucleoside reverse transcriptase inhibitor class [61] and acquired FDA approval for HIV treatment. Benzyl-quinazolin-4-yl-amine belongs to the Epidermal Growth Factor Receptor (EGFR) inhibitor [62]. Camptothecin is an alkaloid in *Camptotheca acuminate*, a part of Chinese traditional medicine, and acts as a Topoisomerase Inhibitor (TOP1 and HIF1A) [63]. And RO-90-7501 is an amyloid-42 aggregation inhibitor and targets the amyloid precursor protein (APP) gene [64]. Amyloid-42 also is a candidate for Alzheimer's disease molecule in humans [65].

5. Discussion and conclusions

From the explorative data mentioned above, the insights in developing potential medicines specified for COVID-19 could be expected for drug companies. Because of the high number for affecting people around the globe, accessing the novel and reliable data seems necessary for researchers and clinicians who are working in this area. Here, we tried to collect the latest computer-simulated data for chemicals interaction with novel coronavirus in addition to molecular analysis information on dysregulated genes in patients. The selected data could be considered as an essential feature for the related upcoming medications and treatment decisions, either as a functional ingredient or as a specific subunit. The best compounds in our report are listed in Tables 1 and 2, and interactions between compounds and viral structures illustrated in Fig. 1. However, referring to the main databases for such information is still required due to the rapid changes in the field. Such sources could be included a broad range of specified pages like those for global research on COVID-19 on WHO website to computational modeling dedicated databases [66] as well as PMDB [67], SWISS-MODEL [68,69], and UniProt [70].

As recently, the investigators started to use simulation and modeling techniques for drug development and efficacy prediction against novel CoV; the pre-existing data proved to be a trustworthy assist for such

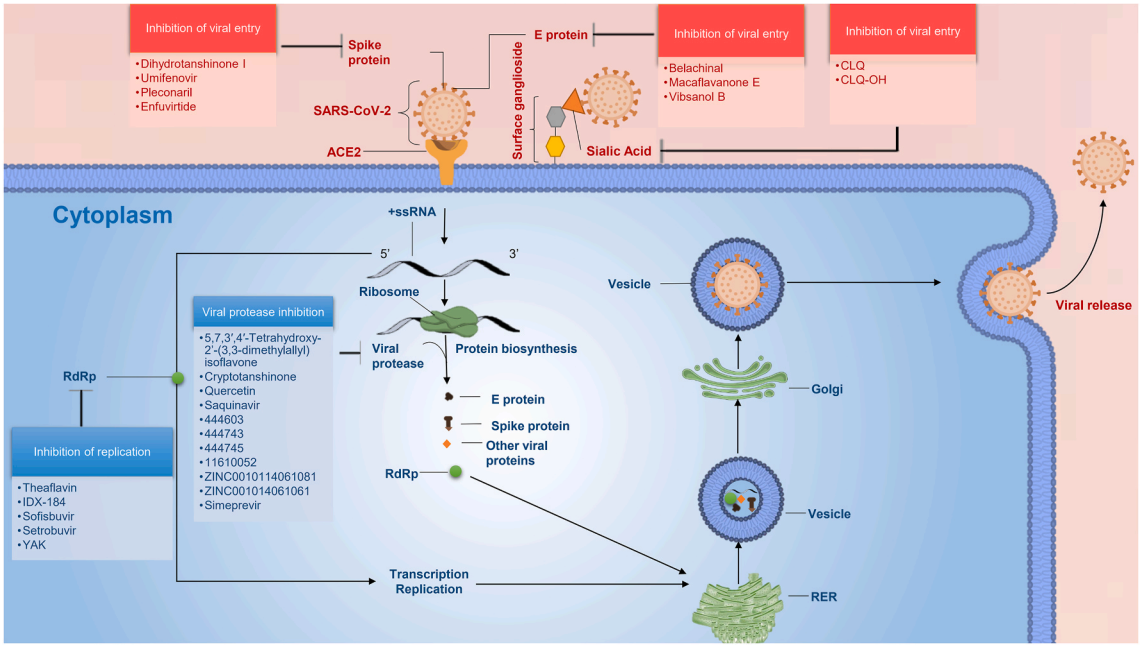

Fig. 1. Interactions between SARS-CoV-2 constitutes and possible therapeutic agents predicted by molecular docking studies. SARS-CoV-2 attaches to whether ACE2 receptor or surface gangliosides with its spike protein. The + ssRNA enters the human cell after attachment. The replication process continues using RdRp. On the other side, viral proteins are biosynthesized and sent to the rough endoplasmic reticulum (RER). Viral proteins and genome combine in a vesicle and then sent to the Golgi. A complete viral structure will be sent to the cell membrane for exocytosis.

research area. Examples include the Verscheijden study that employed modeling and simulation approaches in support of dosage adjustment for CHQ in pediatric COVID-19. As far as such investigations in children won't be possible, to avoid any toxic effects and reach the suboptimal dose recommendation, knowledge-driven and model informed dose selection is applied as a scientific alternative for this goal [71]. Macchiagodena and colleagues also utilized docking and molecular methods to finding any potential non-covalent 3CLpro inhibitor major compounds for SARS-CoV2. The structure-based ligand design and molecular modeling successfully implemented the most suitable docked ligands introduced for SARS-CoV2 main protease with the typical pattern of binding with aromatic moieties, which were connected through rotatable bonds in a pseudo-linear arrangement [72]. Other efforts focused on optimizing the regimen and effective drug repurposing for available medicines for patients with COVID-19. A mechanistic Pharmacokinetic/virologic/QTc model was developed and validated externally to predict the viral load decline in SARS-CoV2 cases successfully [73]. Moreover, Chloroquine, Chloroquine-OH, and Umifenovir (no FDA label) as viral entry inhibitors, Remdesivir (no FDA label), Ribavirin, Lopinavir, Ritonavir, and Darunavir as viral replication inhibitors, and Sirolimus are the other examples of drugs, which were tested clinically on patients after comprehensive assessments of the available data on molecular simulation and target prediction [74,75]. These clinical studies on predicted drugs against COVID-19 can fuel further clinical research based on previous drug-target prediction methods.

In order to fast stopping the COVID-19 pandemic, researchers and medical staff have to find appropriate treatment among currently available compounds as the first step in drug development strategies. Computer simulations via specified free and/or licensed molecular modeling tools like the Swiss-Prot server, Molsoft ICM-browser, and PyMOL, in addition to earlier introduced databases and resources, have also paved the way for testing different compounds on SARS-CoV-2 with high accuracy and sensitivity. Although computer simulations would help us to find the possible therapeutics for COVID-19, they would not be reliable until we perform experimental and clinical studies. Computer simulations are not able to consider all aspects of interactions between drugs and cell/body environment, and what happens in the microscopic scale might be completely different by the way and further in vitro and in vivo studies have to be conducted to confirm compounds' safety and efficacy against COVID-19. A summary of *in silico* investigations of possible natural and synthetic medications presented in the current study and the review provide a better understanding of SARS-CoV-2 genomic and structural characterization compared to other CoVs. This can be a helpful tool for other investigators who are working on drug discovery and development for COVID-19.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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