Geometric Hashing and AI-Quantum Deep Learning functional similarities on Remdesivir, drug synergies to treat COVID-19 in Practice.

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Abstract

Novel SARS coronavirus 2 (SARS-CoV-2) of the family Coronaviridae starting in China and spreading around the world is an enveloped, positive-sense, single-stranded RNA of the genus betacoronavirus encoding the SARS-COV-2 (2019-NCOV, Coronavirus Disease 2019. Remdesivir drug, or GS-5734 lead compound, first described in 2016 as a potential anti-viral agent for Ebola diseade and has also being researched as a potential therapeutic agent against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus that causes coronavirus disease 2019 (COVID-19). Computer-aided drug design (CADD), Structure and Ligand based Drug Repositioning strategies based on parallel docking methodologies have been widely used for both modern drug development and drug repurposing to find effective treatments against this disease. Quantum mechanics, molecular mechanics, molecular dynamics (MD), and combinations have shown superior performance to other drug design approaches providing an unprecedented opportunity in the rational drug development fields and for the developing of innovative drug repositioning methods. We tested 18 phytochemical small molecule libraries and predicted their synergies in COVID-19 (2019- NCOV), to devise therapeutic strategies, repurpose existing ones in order to counteract highly pathogenic SARS-CoV-2 infection. We anticipate that our geometry hashing driven quantum deep learing similarity approaches which is based on separated pairs of short consecutive matching fragments, can be used for the development of anticoronaviral drug combinations in large scale HTS screenings, and to maximize the safety and efficacy of the Remdesivir, Colchicine and Ursolic acid drugs already known to induce synergy with potential therapeutic value or drug repositioning to COVID-19 patients.

Keywords; Deep Learning Quantum mechanics Colchicine Remdesivir Ursolic acid COVID-19

Introduction

In the absence of effective vaccines and drugs to the prevention, treatment and rehabilitation for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectious, many potential therapies including, chemo-immunomodulators, antiviral therapies, supportive interventions, convalescent plasma transfusion, and traditional Chinese medicine (TCM), have been used and have shown promising clinical outcomes. (1) The TCM has been proved as an effective treatment strategy to prevent and control the epidemic, especially in preventing mild symptoms from turning into severe ones. Ancient Indian medicinal scriptures including Atherveda, Phyllanthus emblica, Rig-Veda, Phyllanthus emblica, Vitis vinifera, and (1) Charka Sanhita have been widely used since ancient times are and are well known for boosting the immune system. They are a remarkable natural source of (1,2) high value alkaloids, phenols, flavonoids, coumarines, chalcones, lignans, alkanes, polyketides, alkenes, simple aromatics, Emblicanin B, alkynes, Vitilagin, peptides, Chebulanin, terpenes, Punigluconin and steroids for the treatment of various human aliments and for the increase of the human immunity (1,2) and longevity. Prediction of protein–protein interactions and the structures of the resulting complexes is a key task in Computational Structural Biology. Although experimentally determined structures of complexes are rapidly accumulating, they are far from being able to cover the complete interactome. In the current era of computer-aided drug discovery, enormous medicinal drug likeness properties of ancient plants allows the pharmacists and researchers to exclusively use them for the In-Silico discovery of drug-like natural molecules. Ursolic acid (3-β-3-hydroxy-urs-12-ene-28-

oic-acid) and oleanolic acid (3β-hydroxyolean-12-en-28-oic acid) are pentacyclic triterpenoid compounds and have been isolated from diverse plants, such as Chamaedora tepejilote (1), Ledum groenlandicum (2), Lantana hispida (3), and Uncaria rhynchophylla (4), with a widespread occurrence throughout the plant kingdom (1,2). The problem of recognising an image has been extensively studied in the field of computer vision, pattern recognition, etc. Their antibacterial (1,2,4), antiparasitic (2,3,4), antiviral (1,3,4), antitumor, antioxidant, anti-inflammatory (4), and hepatoprotective therapeutic properties and biological activities have been reported and in-vitro evaluated in human macrophage-models at inhibitory concentrations. Bromodomain protein 4 (BRD4) is a member of the extraterminal (BET) family proteins that binds to acetylated histones through elongation factor b (P-TEFb). The bromodomains act as a reader in cell growth and a writer in cell cycle progression of histone acetylation that plays important roles in different biological processes including memory formation, replication, mitochondrial oxidative phosphorylation, transcription, DNA repair and and DNA damage response (5). In the proposed indexing technique, since each feature point is inserted exactly once, both memory and searching cost has been reduced significantly Molecular structure can be determined in heterodox interpretations by solving the time-independent (11) Schrödinger equation: QM methods, (12) vertex prizes and edge costs including ab initio (13) Density Filed Theories (DFT) and semi-empirical in place of the quantum processor and (14) energy among other observables, (15) under simulated (16) error as well as (17) to reposition drugs (18) about bonding may represent the (19) similarities and dissimilarities (20) between drugs and (21) repurposed viral (22) proteins respectively. (23) However, the Schrödinger equation (24) cannot actually be solved for any (25) but a one- data-driven (26) electron system methods (the hydrogen atom), (27) and approximations (28) need to be made. (29)In this research article (30) we present a drug- repositioning strategy and a Quantum (31,32,33,34,35,36,37) Deep Learning SARS-CoV-2 main protease, Mpro, DPP4 ADABP, ADCP2, CD26, DPPIV, TP103, FURIN, FUR, PACE, PCSK3, FURIN-ADAMTS1-ROR-GAMMA-SRRM2-RORγ- NF-κB/RelA-STAT3A-RORγ- NF-κB/RelA-STAT3B, Nsp15, TCEB2-->ASB8->>TCEB1, ACE2, ACEH angiotensin I converting enzyme 2, Remdesivir, Colchicine and Ursolic acid drugs network-based (13,14,15,18-38) prioritization method based on a (22,24,25,26,28,27) heterogeneous network (28,29,30,31,32,33,34,35,36) integrating similarity to (30,31,32,37,38,39,40,41) combine drugs and herbals that can be used against devastating diseases such as COVID-19 Structural basis of receptor recognition by SARS-CoV-2. Receptor Recognition by the Novel Coronavirus from Wuhan Anti-HCV, nucleotide inhibitors, repurposing against COVID-19 Virtual screening of integrase inhibitors by large scale binding free energy calculations: the SAMPL4 challenge Quantum Chemical Approaches in Structure-Based Virtual Screening and Lead Optimization (30-36). (36,37,38) For indexing, Heterodimer binding scaffolds recognition via the analysis of kinetically hot residues classical geometric hashing maps feature points of an object to hash table with respect to a bases pair points which are selected from the object itself. In order to handle all possible rotations without affecting the performance of the recognition algorithm and without modifying the existing index structures. in this virtuall screening experiment, our technique considers all possible bases pair (effectively nC2, where n is the total number of feature points in the object) and maps object feature points in the hash table with respect to all the bases pairs. (38-41) As a result, direct evaluation of thermal fluctuations in Collected motions using a single-parameter harmonic potential increases both memory and searching cost. In the proposed technique, in order to handle all possible rotations in an object, each image object is aligned using principal components of the feature points obtained using the PCA. (32,37-41) So the technique effectively removes the use of bases pairs extracts the features from a query and preprocessed similar to indexing stage and accesses the previously con- structed hash table for recognition. thus reduces the time complexity by a factor of nC2. Overhead in the proposed technique is the use of PCA which is negligible. (12-42,43,44,45, 46,47,48,49,50) This deep learning drug combination technology by ιμπλεμεντινγ a Geometric Hashing type procedure to predict new (17-43) therapeutic indications for drugs and novel treatments for diseases (18-44,51,52,53,54) has the potential to infer novel combined (2,3,5-17,18,22-45) treatments for COVID-19 diseases (19,21,25,28,30-46) as an evidence-based (19,32,33,34,37, 45,46,47,48,49) drug repurposing AI-COVID-19 tool. (50,51) Structure-based drug design, virtual screening and high-throughput screening employed in this project to identify antiviral leads targeting COVID-19 structural conservations of druggable hot spots in protein-protein interfaces. (52,53,54) Anti-SARS coronavirus 3C-like protease effects of this drug combination of the Remdesivir, Colchicine aand plant-derived Ursolic acid compounds and analogues as multi-inhibitors of viral polymerases. (55,56,57,58) Role of the drug combination of this drug combination of the Remdesivir and Colchicine small molecules with the lopinavir/ritonavir was investigated in the treatment of SARS associated to the initial virological and clinical findings from molecular docking study characterization and inhibition of the main protease of severe acute respiratory syndrome coronaviru Coronavirus COVID-19 (formerly known as Wuhan coronavirus and 2019-nCoV). (59,60,61,62,63,64) In this in-silico drug repurposing and binding free energy comparative analysis

for SARS-CoV-2 Main Proteinase and Spike Proteins, old drugs such as Ursolic acid and Colchicine were categorized as lead compounds for a new disease of SARS coronavirus main proteinase targeting severe acute respiratory syndrome human coronavirus. In this project we developed drug repurposing approaches against SARS-CoV-2 using E-pharmacophore based virtual screening, molecular docking and molecular dynamics with main protease as the target. (66,67,68, 69,70) via Interaction-Energy-Based Learning and Improved Method of Structure-Based Virtual Screening by using a novel multi-modal drug repurposing approach for identification of potent Geometric Hashing co-factors as a general and efficient model-based Enhanced Geometric Hashing recognition drug repurposing scheme.

Materials and Methods

Sequences retrieval and alignment

All structural alignments were performed using the Dali server (http://ekhidna2.biocenter.helsinki.fi/dali/) (Holm, 2020) using clinical and pre-clinical tests (in vitro, in vivo, and in silico) to the largest amount of chemical data in this in silico drug repurposing article. The nCOVSNVs with ID NC_045512 were identified and cross-matched with BLASTp for the COVID-19 virus (SARS-CoV-2) receptor binding domain (RBD) and subdomain-1 (319th to 591st aa) of the spike glycoprotein (bat coronavirus RaTG13) with about 74% sequence identity in the single receptor-binding domain for the up configuration and the S1 protein partial (SARS coronavirus GD322) with 100% sequence identity. Total of 1652 SARS-CoV-2 S protein complete sequence alignments of COVID-19 RBD subdomain-1 (319th to 591st) amino acid available at the (2,3,7-39) NCBI Virus portal were retrieved. We then sought to rank the COVID-19 virus RBD subdomain-1 (319th to 591st) amino acid sequences based on the predicted probability that the RNA folds into the MEA structure with 73.96% sequence identity and not other structures (8,9,12-30) according to the patient's corresponding sample information, dates of sample collections, and geographical locations among others which have shown strong clinical evidence of the presence of SARS-CoV by immunohistochemistry, high-resolution oligonucleotide array, electron microscopy, and real-time reverse transcription-qRT-PCR.

Preparation of the protein structures

Receptor models for the SARS-CoV-2 Mpro were prepared by using the Structure Preparation module of MOE to correct PDB inconsistencies starting from both the 6LU7 crystal structure and the QHD43415 I-Tasser model. This choice was made to take binding site flexibility into account to assign the protonation state at pH = 7.0 through an ensemble docking approach (33,34,35,63) but without the need to perform time-consuming molecular dynamic (MD) simulations to generate reliable conformational ensembles. For this purpose, (1,2,4-6,23) we initially selected the three-dimensional structures of the non-structural proteins of the Nsp3, Nsp5 (PLpro domain), (1-5,6,7-48) Nsp12 (RdRp), the structural Spike proteins, the Nsp15 (endoribonuclease), and the nucleocapsid protein (N protein) between the SARS-CoV-2 Mpro structure and the SARS-CoV Mpro, PDB entry 6LU7 as the best-characterized drug targets among coronaviruses. (2,5,6,7,9-27) For the N protein, we clustered 31 conformations with (11,13,14,29,32) Glu174 present in an opened residue conformation out of a total of 40 ionization states (16,19,21-46,47,48) present in the globular cluster of five protease helices, which is involved through a salt-bridge interaction in modulating the homodimerization of the NMR-derived structure of the (PDB code 6YI3 49) Mpro, mainly between the binding cavities of the Arg4 of one protomer and the Glu290 domains of other to select a short linear peptide subset representative (22,24,26,42,43,46,48) within the protease flexibility. (17,18,21,43,48) The aliphatic carbon atoms from the the closed conformation of the Glu174/Glu166 side chain were prepared as a part of the phosphate binding site and then minimized by keeping the ligand constrained and applying backbone restraints as lead in the binding site to steric clashes with potential inhibitors by removing all water molecules using PyMOL software. All minimizations were performed up to a gradient of 0.1 kcal mol–1 Å–2 in order to precisely define the binding site. The receptor and the ligand were then saved for future use.

Collecting gold-standard pairwise drug combinations

In this study, we focused on pairwise drug combinations on clinically and FDA-approved investigational drugs by assembling the publicly available clinical data sources from the updated human interactome and the multiple commonly used small molecule databases. (23,24) Each approved drug in combinations was required to have the experimentally screening system (25,26) and validated COVID-19 protein target information based on GeneCards and on high-quality PPIs: each EC50, IC50, Ki, or Kd $\leq$ 10 μM. (27,28) Compound name, gene expression data, metabolic

associations, evolutionary analysis, commercial name or generic name of each drug and protein-drug datasets were included and (29,30) standardized by MeSH and UMLS vocabularies (22,28-47) and further transferred to DrugBank ID (30-32) from the DrugBank database (v4.3)40. (21) Chembench High Throughput Screening (qHTS) were applied to identify inhibitors and antagonists of the SARS-CoV Mpro, PDB entry 6LU7signaling pathway by measuring the binding affinities and total docking energies controlled by the Remdesivir ligand as the cofactor into these binding domains (30-38, 40) Low frequency DockThor molecular dynamics simulations also applied and duplicated drug pairs were removed. (40, 42, 44)The Gaussian network cooperative model iGNM 2.0 database was applied for biomolecular structural dynamicsto predict the location of hinge sites and free energy localization spots on 681 unique inter-residue, inter-domain cross-correlations pairwise drug combinations as exctracted from literature-derived low-throughput experiments (46,48) by connecting 362 drugs that are retained. We also compiled clinically reported adverse (30,32,37-47,48) drug–drug interactions (DDIs) data from the (40,42-48) the Therapeutic Target Database (TTD, v4.3.02)41, the PharmGKB database (December 30, 2015) and the FDA approved DrugBank databases using reported binding affinity data such as the dissociation constant (Kd), inhibition constant/potency (Ki), median inhibitory concentration (IC50) $\leq$ 10 μM or median effective concentration (EC50). Drug–Protein target interactions, (42-48) Chemical similarity analysis and (32,35,36-48) Collecting adverse drug–drug interactions of (54,58) FDA approved drug pairs were acquired from the publicly available DrugBank database (v4.3).

Multi-scale network visualization, analysis and inference based on the gene-drug networks. (46,47,57) A networkof a large group of viruses using a denormalized tree structure is constructed by entering ORF IDs, GI numbers, and KEGG pathway IDs associated with a number of human respiratory infections combined to the databases of the SARS patients from Hong Kong (n = 1755), Beijing (n = 917) and Taiwan (n = 664) for an arbitrary number of genes, and using data obtained by one or any combination of methods of viral therapeutics and biointerventions (48,57). Nodes based on an integrated dataset with 3,336 SARS patients from Hong Kong, Beijing and Taiwan as corresponding to the selected SARS- CoV-2 main protease, Mpro, DPP4 ADABP, ADCP2, CD26, DPPIV, TP103, FURIN FUR, PACE, PCSK3,FURIN-ADAMTS1-ROR-GAMMA- SRRM2-RORγ- NF-κB/RelA-STAT3A- RORγ- NF-κB/RelA-STAT3B, Nsp15, genes using appropriate software functions were expanded into an increasingly complex set of interactions to discover effective therapeutic agents. Such multi-scale hypergeometric test-based algorithm VisANT visualization of this SARS- CoV-2 schema was used to classify the groups of the TP103, FURIN FUR, PACE,PCSK3, FURIN-ADAMTS1-ROR-GAMMA-SRRM2-RORγ- NF-κB/RelA-STAT3A-RORγ- NF-κB/RelA-STAT3B, Nsp15, TCEB2-->ASB8-->>TCEB1 selected genes as biological network modules to allow quick identification of the shared functions of the given gene set thereby reducing the size of this network to a manageable level, and greatly facilitating the analysis of gene-to-gene, drug-to-drug and gene-to-drug relationships (47,48,49).

Gene Ontology (GO) similarity analysis and Clinical similarity of drug pair analysis
The Gene Ontology (GO) annotation for all the drug-gene targets of the SARS- CoV-2 main protease, Mpro, DPP4 ADABP, ADCP2, CD26, DPPIV, TP103, FURIN FUR, PACE, PCSK3,FURIN-ADAMTS1-ROR-GAMMA- SRRM2-RORγ- NF-κB/RelA-STAT3A- RORγ- NF-κB/RelA-STAT3B, Nsp15, TCEB2-->ASB8-->>TCEB1 coding genes was downloaded from the website: http://www.geneontology.org/. We used three types of the experimentally validated or (4,5,7-22,48) literature-derived evidences (32,33,36-48) biological processes (BP), (31,32-48) molecular function (MF), (37,39,4,42-45) and cellular component (CC), (37-48) excluding annotations inferred (36-47,48) computationally. The semantic comparison of GO annotations offers quantitative (32, 48) ways to compute similarities between (22,27,45) genes and drug-gene (22,48) combination theapy products. The overall GO similarity of the drug target-SARS-CoV-2 main protease, Mpro, DPP4 ADABP, ADCP2, CD26, DPPIV, TP103, FURIN FUR, PACE,PCSK3, FURIN-ADAMTS1-ROR-GAMMA-SRRM2-RORγ- NF-κB/RelA-STAT3A-RORγ- NF-κB/RelA-STAT3B, Nsp15, TCEB2-->ASB8-->>TCEB1 coding genes binding to the Remdesivir, Colchicine and Ursolic acid drugs was determined by Eq. ($x^{\cdot}=f(x,t,\eta),x(t0)=x0(\eta)$ $D=\{(tk,y\sim k)\}k=1nt$ $y\sim ik=yi(tk)+\varepsilon ik,\varepsilon ik\sim N0,\sigma i2(y\sim ik-yi(tk))22\sigma i2$, $p(\theta\ D)=p(D\ \theta)p(\theta)p(D)$ $p(D\ \theta)1\beta lp(\theta)$ $\sigma10\ \sigma20$, averaging all pairs of protein target-SARS-CoV-2 main protease, Mpro, DPP4, ADABP, ADCP2, CD26, DPPIV, TP103, FURIN FUR, PACE, PCSK3, FURIN-ADAMTS1-ROR-GAMMA-SRRM2-RORγ- NF-κB/RelA-STAT3A-RORγ- FURIN-LRP1-MMP17-MMP2-MMP25-NF-κB/RelA-STAT3B, Nsp15, TCEB2-->ASB8-->>TCEB1 coding genesa and b with $\in$ and $\in \langle GO \rangle$

=1pairs∑{p(D θ)=∏i=1ny∏k=1nt1 σi2πexp},GO(,p(θ D)=p(D θ)p(θ)p(D) p(D θ)1βlp(θ) σ10 σ20)(6).

Preparation of the datasets with known e-Drug3D drugs

The dataset containing the (5,7,9) FDA-approved drugs and active metabolites was constructed from the e-Drug3D commercial small molecule and fragments of 1305 different FDA-approved drugs that currently contains 1519 annotated 3D structures of molecular weight <2000 that are represented by a single conformation dataset, (10,12,14) a dataset updated annually and freely available for the scientific community at https://chemoinfo.ipmc.cnrs.fr/MOLDB/index.php (13,15,48). In this In-Silico effort we prepared mol2 files of the essential dataset of the chemical structures from the two supplementary e-Drug3D collections which were carefully constructed and have been shown similar inhibition in infectious models and resulting from (i) the generation of multiple conformers of high-quality and curated structures of FDA-approved drugs with molecular weight less than 2000 for the: {(5-(1lambda4,3lambda4,7lambda4-purin-6-ylsulfanyl)-1-methyl-4H-1lambda5-imidazol-4-ylidene)(oxo)imino}-lambda1-oxidanylidene-heptahydrogen ring systems and (ii) the calculation of the most probable ionic and tautomeric states at pH 7.4. Smaller drugs (backbone with less than 20 heavy atoms) were also prepared in the .pdb, .pdbqt and .mol2 format files (27-42,46) present in the e-Drug3D dataset. (28,30-48) The ensemble of 3D molecule conformations (31,32,45,48) of the larger drugs from e-Drug3D were provided on a separated drug library dataset.

Drugs under clinical trials (COVID-19 repurposing dataset)

Our approach was focused on identifying a cluster of (1-8,13) similar chemotypes followed by parallel docking grid generation using the advanced to the next MM-PBSA-WSAS, KNIME-HTS-HVS filter, and chemical structure preparation wizard as provided by the BiogenetoligandorolTM cluster of algorithms that had the potential to target the (2-8,29) FURIN-ADAMTS1-ROR-GAMMA-SARS-COV-2 conserved domains and fit the geometric constraints without any restraints or constraints when filling in the open valence of the SARS-COV-2-ACE2-RORγ-BRD4-FURIN (30,41) binding pocket residues. These were then (6-48) converted into substructure searches of one copy of SARS-CoV-2 main protease (7-45) which were used to mine commercially available (8-42) compounds and covalently bonded SARS-COV-2 inhibitors using the (9,26,27,32) eMolecules database. The dataset of the selected hit drugs followed the force field parameters as applied to the partial atomic charges of the selectred ligands which were derived using the RESP and collected from published articles (7,38) and approved drugs listed on the (2-39) DrugBank database in the "Clinical Trial Summary by Drug" section to fit the HF/6-31G* electrostatic potentials generated using the Gaussian 16 software package. (6,18,19,21) We intended to generate these from two different branches to model the viral protein using the isotropic position scaling algorithm. (16,28) One branch of the selected hit elements was refered to as the “Remdesivir Literature Substructures” branch, (8,11,37) which was based on the Remdesivir, Colchicine and Ursolic acid substructures using the Antechamber module as extracted (15,26,51) from published bromodomain inhibitors.

Structure-Based Pharmacophore, Docking, Machine Learning (QSAR) Methods.

Molecular docking, quantum mechanical LigandorolTM-inspired physarum-prize-collecting Neural Matrix Factorizations (7,12,13) and drug repositioning scoring and constrained analysis using the SHAKE algorithm were implemented (13-14) to a collection of the (14,15,24) ZINC databases. (12,19,21) Protein-molecule complexes, followed by structural relaxation (13-22) for the cocrystal ligand of SARS-CoV-2 main protease, N3 were generated through (17,18,25) flexible-ligand:rigid-receptor (19) The molecular (4) docking in this local energy minimization of the equations of motion was conducted at a time step of 1 fs to optimize (15) protein-molecule (22,24,32) interactions for the relaxation phase and 2 fs capping (24-27) for the N- and C-terminal of each (26) fragment. i-GEMDOCK (26-27) software deployed at 298 K, 1 bar for 10 ns for the equilibrium and sampling phases through cycles in amino-acids 15-23+ within 4 Å to calculate the full electrostatic energy of any (27,28) docked molecule. In addition, following our (37,38) static analysis, we conducted some (33,34,39) preliminary molecular dynamics studies (39,40,41) on a potential “latch” for the Down state protomer. Ligands were prepared using force field OPLS3e and possible states were generated from pH 7.0±2.0. Docking scores are reported in kcal/mol, the more negative the number, the better binding. The surface glycoprotein (Wuhan seafood market pneumonia virus) (Sequence ID: YP_009724390.1) structure was modeled using ModBase (9) which utilized Modeller (10) for the structural modeling. The sequence (NCBI Accession: YP_009724390) was uploaded to the ModBase interface and was run with the template being SARS spike protein receptor binding domain (PDB: 6XS6 SARS-CoV-2 Spike SARS-COV-2 Main Protease With Unliganded Active Site (2019-NCOV,

Coronavirus Disease 2019,variant, minus RBD). (38,42,43) Explicit solvent molecular dynamics (MD) (28,39,42) in both the minimization and MD simulation stages of novel coronavirus spike protein (42-43) were performed (44,45,) using the NAMD2 program (32,45,51). We used the CHARMM-Gui (46) with the CHARMM36m force field (47-48) along with TIP3P water molecules to explicitly (30-39,44) solvate the proteins of a unit cell in a macroscopic lattice and add any (32,43,55) missing residues of repeating images from the experimental structure atom files selected from the sampled snapshots. (45) Simulations were carried out (35,45,55) maintaining the number of simulated particles, (27,48,56) pressure and temperature (the NPT ensemble) (11,12,41) constant with the Langevin piston method (23,39,57) specifically used to maintain a constant pressure of 1atm. (12,42) We employed periodic (18,44,50) docking boundary conditions to enrich repurposing drug candidates (20,43,49) using a more accurate and more efficient method, the Biogeneto-ligandorolTMQMM-PBSA-WSAS pipeline for a water box simulation (43,49,50) volume as well as the particle nanomesh (24,45,46) Ewald (PME) method with a 20 Å cutoff distances (24,46,49) between the simulated SARS-COV-2 protein (16,47,48,54) and water box edge since the most chemical ligands and herbals comprising antiviral and antibacterial activities are large and consist of many rotatable bonds. The integration time entropy step was 2 femtoseconds using a method coined WSAS (weighted solvent accessible surface area) with our protein simulations (17,48,55) as conducted under physiological conditions (37 C, pH of 7.4, (56,60) physiological ionic strength) based on the MM-PBSA-WSAS binding free energies. To emphasize the (8,9,57,60) computational efficiency of the method (9,10-46) we would like to mention that the average computing time (14,15,58) for one solution was <10 s on a single GPU processor by using solvent assessible surface area, 0.054. (47,56) A significant variability in the solutions can be observed. (27,37,38,39). The docking calculation (21,23,33) for estimating the nonpolar solvation energy was performed on the prepared dataset of 195 SARS-COV-2 receptors and FDA ligands by using the Biogeneto-ligandorolTM Cluster of docking softwares and workflows based on default parameters.

Filtering, refinement and Hash Table Generation

In this research project the refined binding poses were computed based on local SARS-CoV-2 RBD structural alignment in the vicinity of the template binding site, producing potential complexes that are physically possible with acceptable steric clashes among SARS-CoV-2, SARS-CoV and RaTG13 in hACE2 in a clustered pharmacophoric model mapped into the location pl of hash table by placing the midpoint of the co-ordinate system at the center of the hash table as follows pl = f l +size(H)(1) where size(H) is the number of bins in the hash table from different strains complexed with ACE2 from different hosts. (30,64) To filter out the undesired results, we test for clashes using a distance transform grid, similar to the one applied after mapping, all feature points are inserted into hash table as H(pl) = H(pl)∪(Mid,D) where Mid and D are the model identity and the descriptor vector of the feature point respectively. (24,31,65) The same process is repeated for each model in the database. B If the distance is above a predefined penetration threshold (5 Å), the result is rejected. Searching In contrast to classical geometric hashing, the response time in the enhanced geometric hashing is much faster because it needs to compare with a smaller number of feature points. (33,64) For a query Q, Algorithm 2 gets the top k best matches from the hash table in a two step process, filtering and the filtering step, the feature points which are di query's feature points are filtered out while at re the top k matches are found based on the votin1). (53,65) In the filtering ture points of the model which are dissimilar feature points were filtered out based on their de D geometric complementarity score is calculated It can be noted that the feature points of images of the same model may be missed du present in the images favouring shape complementarity and penalizes the remaining steric clashes. In order to improve the performance, it considers the feature points not mapped bin but also from its nearest bins of si. Let {f1, f2, · · ·, fn} be the n feature points For a feature point, fi, let q be the mapped ind table H. As discussed above, it is considered Kof q in H. Let z be such a neighboring bin, K2, q+K2.(57,66) Note that there may be some fe different models from the database lying in the bc be a feature point of a model lying in z. Eucl. between q and c, $\forall c \in H(z)$ and $z \in q - K2$ During indexing, the features f1, f 2, .., fm are extracted for all models using SURFalgorithm (19). (67)There is a possibility that the model images may appear translated and rotated relative to their original positions may not have the same scale. Hence in order to make the proposed indexing technique invariant to translation, rotation and scaling, this pharmacophoric model of the selected hit candidates as exctracted from the screen database was preprocessed. (64,65,66,67) It consists of three steps, mean centering, rotation with respect to principal components and normalization were obtained by $d(c) = ||D(q) - D(c)||$A candidate pharmacophoric set of the Remdesivir, Ursolic acid and Colchicine Ci ligands for the corresponding feat the query Q contains all the model identity Mi $d(c) \leq t$, $\forall c \in H(z)$ and $z \in q - K2$, q +is the assigned threshold. The same procedure i all query points f1, f2, · · ·, fn. Thus, there ar sets C1, C2, · · ·, Cn for given n feature points In refinement step, these candidate sets C1, C (67,68,69,70).

Binding free energy calculation and In silico screening

Before binding free energy calculation, the Sander module in Amber16 (26) program was used to perform the three-step optimization of the ligand-receptor complex. Firstly, only waters, ions and hydrogens were allowed to move. Secondly, the backbone atoms of the protein were fixed while others were allowed to move. Thirdly, all the atoms of the system were free to move. In the three optimization process, 2000 steps steepest descent method followed by 2000 steps conjugated gradient method based on their de D geometric complementarity score were used for each ligand-receptor binding system. Finally, the binding free enegy (ΔGbind) is calculated by using the MM/PBSA (27, 28) and X-score methods (29, 30). As for the X-score method, it is assumed that the overall binding free energy rotated relative to their original positions in a protein-ligand binding process can be divided into several terms (31). Here, ΔGvdw represents the van der Waals interaction between the receptor and the ligand; ΔGH-bond represents the hydrogen bonding between the receptor and the ligand; ΔGdeformation represents the deformation effect; ΔGhydrophobic represents the hydrophobic effect; ΔG0 represents a regression constant. (32,33) ΔGbind and absolute binding free energy ΔG◦b values between the receptor and the selected hit candidates could be calculated simply by the X-score software package in Quantifying Magnetic Sensitivity Radical Pair Based Compass Quantum Fisher Information: H=γB·(Sˆ1+Sˆ2)+Iˆ·A·Sˆ2, Sˆi=(σx,σy,σz) Iˆ ρs(t)=TrI(U(t)ρ(0)U†(t)), Uλ(r) = U0(r) + λu(r), ρI(0)=I/2 employing a λ-dependent effective potential energy function P(t′)=dΔM(t′) ΔM=f(t ′)dt′,ρ¯s=∫−∞0f(t′)ρs(t′)dt′=∫0∞f(t)ρs(t)dt, where r = (rA, rB) denotes the atomic coordinates U0(r) = U(rA) + U(rB) ∫−∞0f(t′)dt′=∫0 u(r) = u(rA, rB) = U(rA, rB) − U(rA) − U(rB) ∞f(t)dt=1 ρ¯s ρ¯s ρ¯s ρ¯s (0,π/2)ρ¯sρs(0)ρ¯sQFI≈∑i=01Re(ρi12)2 for each conformation r = (rB, rA) (1ρi11+1ρi22)+ (ρi11−ρi22)2ρi11+ρi22, of the form u′(r)={umaxtanh(u(r)umax),u(r)u(r)>0u(r)≤0,
where umax is some large positive value ρ1ij=〈φi|〈1|ρs(0)|φj〉|1〉 between the effective potential energies U(r) with implicit solvation of the form ρ0ij=〈φi|〈0|ρs(0)|φj〉|0〉 |0〉 |1〉 H1=γB0·Sˆ1 Re(ρi12) ρi12 ρs(0) ρ¯s |S〉=12(|10〉−|01〉)2Gdeformation+ΔGhydrophobic+ΔG01 (29,33,34). In the MM/PBSA method (32), the free energy of the receptor/protein-inhibitor binding, ΔGbind, was obtained from the difference between the free energies of the receptor/protein-ligand complex (Gcpx) and the unbound receptor/protein (Grec) and ligand (Glig). The binding free energy (ΔGbind) was evaluated as a sum of the changes in the binding energy (ΔEbind), solvation entropy (−TΔSsol), and conformational entropy (−TΔSconf) (shown in Eq. 2) (33,34,59). Where ΔEbind is interaction energies between the three .pdbqt data sets with respect to principal components and normalization which were obtained by d(c) = ||D (q) − D (c)||A for the pharmacophoric set of the Remdesivir, Ursolic acid and Colchicine Ci small molecules and the SARS-CoV-2 protein targets, which were computed using the Sander modules of the Amber16 program. The entropy contribution to the binding free energy (−TΔS) was obtained by using a local program developed in our own laboratory (33,34). ΔGbind=ΔEbind−TΔSsol−TΔSconf.

Results

In this drug combination In-Silico project, a comparative parallel docking analysis of the S protein has been performed and the selected ligands that had docking scores better than −60.5 kcal/mol with one reference strain were selected as the hit candidates for each CoV type and thereby taking into account only the most prevalent residue harbored at the conserved given positions. (Figures1a,1b,2) SARS-COV-2 Immunity Interaction 3D Map sequence allignement analysis and a Multiple sequence alignment of all the HCoV strains (COVID19 genes of (ACBD5, ACE2, ACO2, ACSL3, ADAM9, ADAMTS1, ADAR, AGPS, AGT, AGTR1, AGTR2, AKAP8, AKAP8L, AKAP9, ALG11, ALG5, ALG8, ANO6, ANPEP, ANTXR1, ANTXR2, ANXA2, 7AAP_D, 7AAP_C, 7AAP_B, 7AAP_A, 6ZRU_A, 6ZRT_A, 7K40_A, 7K3T_A, 7K1O_C, 7K1O_B, 7K1O_A, 7K1L_B, 7K1L_A, 7JZU_B, 7JZN_C, 7JZN_B, 7JZN_A, 7JZM_B, 7JZL_B, 7JZL_C, 7JZL_A, 7JX6_B, 7JX6_A, 7JKV_B, 7JKV_A, 7D1O_A, 7CAK_C, 7CAK_B, 7CAK_A, 7CAI_C, 7CAI_B, 7CAI_A, 7A98_C, 7A98_B, 7A98_A, 6ZXN_C, 6ZXN_B, 6ZXN_A, 7A97_C,, 7A97_B, 7A97_A, 7A96_C, 7A96_B, 7A96_A, 7A95_C, 7A95_B, 7A95_A, 7A94_C, 7A94_B, 7A94_A, 7A93_C, 7A93_B, 7A93_A, 7CMD_D, 7CMD_C, 7CMD_B, 7CMD_A, 7CJD_C, 7CJD_B, 7CJD_A, 7CJD_D, 6ZOK_j, 6ZOJ_j, 6XMK_B, 6XMK_A, 6Z97_C, 6Z97_B, 6Z97_A, 6YOR_A, 6YOR_E, 7JZ0_Dl, 7JZ0_C, 7JZ0_B, 7JZ0_A, 7JYY_D) in the SARS-COV-2 RdRp sequences were applied to the MEP1B-MEP1A-FN1-MDN1-UBC-MRPS5-FURIN-ADAMTS1-ROR-GAMMA pathways. To analyze this, we employed the conservation analysis using the total number of protein sequences treated for each CoV type using the reliable BiogenetoligandorolTMQMM-PBSA-WSAS binding free energy HTS-HVS strategy. The Ursolic acid small molecule when combined with the Remdesivir chemical structure generated Salt Bridges into the amino acid of the 836 ARG A 18 U P 4.57 Phosphate with the docking energies of

the 8240,8240,8243,8228,8241,8242 84.767, 82.285, 113.039 88.794, 80.678, 111.585 849Kcal/mol. It also interacted with Hydrogen bonds inside the amino acid of the LYS A 17 U P 4.64 with the docking energies of the 8220,8220,8205,8222,8223,8221 81.688, 84.935, 117.166 84.063, 86.886, 120.648Kcal/mol. The Remdesivir, Colchicine and Ursolic acid drugs bind into the SD1 stands the most conserved druggable domain among all four Beta-CoVs analyzed. The Remdesivir small molecule when combined to the Ursolic acid and Colchicine chemical structures binds inside the amino acid 287 LEU A 9000 6Q5 A 3.99 3849 200 -19.472, 23.825, -15.927 -15.959, 22.345, -17.092 + 323 HIS A 9000 6Q5 A 3.56 3848 516 -25.010, 21.669, -15.561 -24.824, 21.905, -12.016 (Supp.Material). Each separate analysis returned positive results (Tables1, 3a, 3b, 3c), (FigureS2, and FigureSs3a, 3b, 3c, 3d, 3e, 4a, 4b), indicating that the Recomborovir compounds may directly inhibit 2019-nCoV. The Remdesivir, Colchicine and Ursolic acid small molecules are targeting the PLpro (M2, M3, M7, M9, M10, M11 and M13) dinding domains in the amino acids of the 164 HIS A 5 PJE C 2.16 3.07 153.73 2408 N3 1266 O2 with the docking energy values of the -12.282, 14.994, 67.123 -15.161,15.336, 68.144 in the region between the thumb and palm of the amino acid of the 144 SER A 803 DMS A 3.66 3.99 102.68 1114 O3 4736 O2 with the docking energies of the 35.403, -33.742, -8.029 37.550, - 32.180, -11.001 , which might interfere with substrate entering this enzyme's active | 166 GLU A 803 DMS A 5.01 Sulfonium 4735 36.185, -32.686, - 7.387 36.922, -36.568, -4.314 sites, located at the bottom of the two domains (29). This molecule combination named Recomborovir reported to inhibit the 3CLpro (M1, M2, M3, M4, M5, M7, M8, M10, M11, M12 and M13) mainly entered the region between domains 2 and 3, and this 295 ASP A 813, DMS A 5.38 Sulfonium 4739 35.134, -46.698, -27.502 30.989, -48.448, -24.558 region is important for 3CLpro to form a dimmer (30). Recomborovir was reported to inhibit viral entry, accordingly it bound the fusion cone of spike protein; this cone structure is important for viral membrane fusion (31) (Tables1a,1b,2). The Ursolic acid when in-silico combined with the Remdesivir and Colchicine small molecules generated Hydrogen bonds, Salt bridges and Metal complexes inside the POP composite and Diphosphate, dihydrogen ION binding sites into the 7bv2 protein targets. This drug combination of the Remdesivir, Colchicine and Ursolic acid generated also pi-Cation Interactions inside the A 101 F86 P 3.61 1.61 binding cavities of the amino acid of the 555 ARG with the docking energy values of the (8618, 8608, 8610, 8621, 8625 90.830, 92.165, 105.289, 93.435, 92.714, 107.732) Kcal/Mol. It also constructed 10 G P 1005 Metal Complexes targeting the MG atom 8283 with the bond energy values of the (12.33, 92.442, 84.162, 100.658, 90.927, 83.719, 102.373) Kcal/Mol (Tables3a,3b,3c). This Recomborovir drug combination targets the backbone of the Leu278− Gly279− Ile280 loop which is coordinating the P+2 (Asp) side chain, while P+1 (Ser) side chain is coordinated by the Ile280 carbonyl. This interaction was further strengthened by the backbone interaction between the amide hydrogen-carbonyl of the Recomborovir compounds at Gly284 and the P−3 (Ile) carbo-nyl/amide hydrogen. (FigureS5a) Hydrophobic interactions of the combination of the Remdesivir, Ursolic acid and Colchicine small molecules generated 02J (5-Methylisoxazole-3-carboxylic acid) binding sites into the 6LU7 protein targets. The interactions that established after docking the Colchicine small molecule against COVID-19 02J (5-Methylisoxazole-3-carboxylic acid) RdRp were confirmed the behavior of this drug combination inside this hydrophobic surface.(FigureS4d) ZN-A-1002 Ion Metal complexes including attractive solute-water interactions were established after docking the Ursolic acid small molecule onto the COVID-19 7BV2 Interacting A chains of the amino acid of the 295A, HIS, (FigureS4c) inside the ZN-A-1001 Ion 1: Zn, tetrahedral (4)1, binding sites into the 7BV2 protein targets with the docking energies of the (8594, 1771, 2.09, 2, 301A, 8594, 1816, 2.31) Kcal Mol. Metal Complexes were also observed in the 3, 306A, 645A, CYS, 646A, CYS, that sterically permitted water layer binding pockets inside the ZN-A-1002, 1: Zn, tetrahedral (4), 1, 487A, binding domains of the amino acid of the 310A, CYS, with the docking energies of the (8594, 1857, 2.31, 4, 8594, 1889, 2.31, 8595, 3297, 2.38, 2, 642, 8595, 4527, 1.87, 3, 8595, 4550, 2.3, 4, 8595, 4556, 2.34)Kcal/Mol. (FigureS4e) Idealized -U-U-A-U-A-A-C-U-U-A-A-U-C hydrophobic flat surfaces, were localized to a narrow central region between the Ursolic acid ligand and G-A-U-U-A-A-G-U-U-A-U-F86-MG residues, with U composites containing Uridine Monophosphate binding sites when docked into the 7BV2 protein targets. (FigureS4f) Hydrophobic anions associated with G-A-U-U-A-A-G-U-U-A-U-F86-MG hydrophobic pockets containing Guanosine Monophosphate binding sites were generated when the Ursolic acid small molecule combined with the Remdesivir small molecule and reverse docked onto the 7BV2 G-A-U-U-A-A-G-U-U-A-U-F86-MG binding pockets inside the (Nam), (O3), 3752 (O2), 8324 (O2), binding sites of the amino acid of the 4507A, ASN with the docking energies of the (2.58, 3.43, 143.55, 3450, 5, 543A, ASN, 3.04, 3.54, 113.10, 8313) Kcal/mol. Studies of hydrophilic, hydrophobic interactions of the Remdesivir drug when combined to the Colchicine small molecule

indicated to us that the combination of these drugs generated self-assembled monolayers of the 1: Mg, NA (1), 1, 10P, G Metal Complexes inside the 1,553A binding cavities of the amino acid of the ARG into the 7bv2 protein targets with the docking energies of the (8606, 8283, 2.33, 5.33, 8596, 8596, 8597, 8598, 8599, 8600) Kcal/mol. (FigureS5b) Hydrogen bonds, Salt bridges and Metal complexes of the Ursolic acid ligand containing POP Phosphate composites were constructed when docked into the Diphosphate, dihydrogen ION PJE:C:5, 010:C:6, binding sites when combined with the Colchicine drug into the same 6LU7 protein targets at the presence of hydroxy groups at both channel-portals means that co-bound waters at exceptionally high docking energies. The Hydrophobic Interactions that established after docking the Colchicine ligand when computationally combined with the Remdesivir and Ursolic acid small molecules against the COVID-19 PJE:C:5, 010:C:6, RdRp binding sites near both repulsive and attractive hydrophobic surfaces are larger than the Lopinavir/Ritonavir molecular complexes at the water-vapor interface inside when docked onto the binding cavities of the amino acid of the 25A, THR, with the docking energies of the (3.73, 2415, 179) Kcal/mol. (FigureS5c) The Remdesivir binding site's in 5X8S protein targets are more entropically favored contribute to a destabilization of water structure when generating Hydrophobic Interactions, Hydrogen Bonds, Water Bridges and Salt Bridges within the 6Q5-A-9000 Interacting chains. More specifically, the Remdesivir small molecule generated Water Bridges inside the binding domains of the 1286A GL (O2), N, (O.co2), with the docking energies of the (3.86, 2.74, 109.20, 83.72, 3841, 192) Kcal/mol when combined with the Ursolic acid and Colchicine ligands. (FigureS5d). Aditionally, Hydrophobic Interactions, Hydrogen Bonds, Water Bridges and Salt Bridges constructed when the Remdesivir docked in combination with the Ursolic acid small molecule onto the 6Q5-A-9000 Interacting chains into the 5X8S protein targets of the residues of the 1479B, HIS 3898 (O3), 3684 (N2), with the docking energies of the (1.92, 2.69, 134.37)Kcal/mol.

Discussions

In this research report, we found that the Cluster of the Recomborovir-(Drug Combination) which was identified during screening of a compound diversity set performed by the Biogeneto- ligandorolTM cluster of algorithms on the intersection track of the (Lys711 and Arg355/SARS-CoV2 PLpro and Lys711 and Arg355 amino acids. The Remdesivir, Colchicine and Ursolic acid drugs bind into the SD1 which stands the most conserved druggable domain among all four Beta-CoVs analyzed. The Remdesivir small molecule when combined to the Ursolic acid and Colchicine chemical structures binds inside the amino acid 287 LEU A 9000 6Q5 A 3.99 3849 200 -19.472, 23.825, -15.927 -15.959, 22.345, -17.092 + 323 HIS A 9000 6Q5 A 3.56 3848 516 -25.010, 21.669, -15.561 -24.824, 21.905, -12.016 (Supp.Material), (FigureSs1a,1b,2,3a,3b,3c,3d,3e). Each separate analysis returned positive results (Tables1,3a, 3b, 3c)(FigureS2, and FigureSs3a, 3b, 3c, 3d, 3e, 4a, 4b), indicating that the Recomborovir compounds selected may directly inhibit the 2019-nCoV. The Remdesivir, Colchicine and Ursolic acid small molecules targeting the PLpro (M2, M3, M7, M9, M10, M11 and M13) dinding domains in the amino acid of the 164 HIS A5, PJE C2, with the docking energies of the 16 3.07 153.73 2408 inside the atoms of the N3 and O2 with the docking energy values of the (-12.282, 14.994, 67.12315.161,15.336, 68.144) Kcal/mol in the region between the thumb and palm of the amino acid of the 144 SER A 803 DMS A O3, O2 with the docking energies of the (3.66 3.99 102.68 1114 4736, 35.403, -33.742, -8.029 37.550, - 32.180, -11.001)Kcal/mol which might interfere with substrate entering this enzyme's active binding domains of the amino acid of the 166 GLU A 803 DMS A 5.01. The Sulfonium sub-surfaces interacted with the combination of the Recomborovir drugs with the docking energies of the (4735 36.185, -32.686, - 7.387 36.922, -36.568, -4.314)Kcal/mol inside the binding sites, located at the bottom of the two domains (29). This molecule combination named Recomborovir reported to interact with negatiove docking energy values inside the 3CLpro (M1, M2, M3, M4, M5, M7, M8, M10, M11, M12 and M13) mainly entered the region between domains 2 and 3, and this 295 ASP A 813 DMS A 5.38. The same drug combination generated Sulfonium bondings with energy values of the (4739 35.134, -46.698,-27.502 30.989, -48.448, -24.558) Kcal/mol onto the same region which is important for 3CLpro to form a dimmer (30). Recomborovir was also reported to interact with the SARS-COV-2 viral invasion pathways, when it bound the fusion cone of spike protein, the cone structure which is important for viral membrane fusion (31) (Supp.Material). The Ursolic acid when combined with the Remdesivir and Colchicine small molecules generated Hydrogen bonds, Salt bridges and Metal complexes of the POP (composite ligand, containing Diphosphate, dihydrogen) ION binding sites into the 7bv2 protein targets. The chemical strucutures of the Remdesivir, Colchicine and Ursolic acid) targeting into the Lys711 and Arg355 residues and inside the residues of the Phe19, Trp23, and Leu26, which are located in an alpha-helical region of the SARS- CoV2 PLpro N terminus that binds to the N-terminal Lys711 and Arg355 hydrophobic pocket (17). The druggable scaffold of this drug combination of the Remdesivir,

Colchicine and Ursolic acid small molecules target into the binding domaisn of these three critical SARS-CoV2 PLpro residues; the combination of the hit compounds therefore competes with endogenous SARS-CoV2 PLpro for binding to Lys711 and Arg355. In this In Silico Drug repurposing project, we created a new track to display the contacts of this drug combination with each of those: Lys711 and Arg355, and SARS-CoV2 PLpro. Interestingly, this drug combination consisted of the Remdesivir, Colchicine and Ursolic acid chemical structures targets the Lys711 and Arg355 homo-dimerization site and intersects within the Lys711 and Arg355- Recomborovir-(Drug Combination) binding sites, suggesting that they may also interfere within the binding pockets of the Lys711 and Arg355 homodimerizations.The key residues of the seven hot spot binding domains that contribute to S spike glycoprotein trimerization can be potentially In-Silico dow-regulated by the docking combination of the therapeutic agents of the Remdesivir, Colchicine and Ursolic acid drugs in order to significantly block the quaternary structure assembly of the SARS-CoV-2 replication protein. Furthermore, the combination of the drugs of the Remdesivir, Colchicine and Ursolic acid targets the BRD4, JQ-1, ISG15, IFN-β, IL-1β, I-BET 151 and OTX-015 exhibited viral inhibition with a short hairpin RNA (shRNA; shBRD4) which is involved in the recognition of molecular patterns and mediate severe inflammatory responses, may also interact within the binding domains of the S protein via 10 active residues located in the S1 subunit. I also suggested that the Recomborovir-(Drug Combination of the Colchicine, Remdesivir and Ursolic acid) might interact with this ganglioside-binding domain within the S protein (61). Drug repurposing or the chemical optimization of existing drugs represent an effective drug discovery approach and Drug Combination therapeutic approach which has the potential to reduce the time and costs associated to the de novo drug discovery and development of this anti-COVID-19 clinical trial process (59,60,61). This In-silico project demonstrated that the combination of the drugs of the Remdesivir, Colchicine and Ursolic acid can potentially inhibit the SARS-CoV-2 replication (60), (61). Additionally, the GEMDOCK algorithm cannot determine binding free energies or binding orientations of small molecule combinations. For that aim, other docking tools and Geometry Hashing driven Mi $d(c) \leq t,\ \forall c \in H(z)$ and $z \in q - K2, q +$ molecular dynamics studies were applied, as explained above. Therefore, the BiogenetoligandorolTM approach that takes a multiple-sequence-conserved alignment (coMSA) in .pdbqt format file as an input is mainly aimed at binding residues recognition in cases on QMMM homology modeling techniques where the binding partner is a small chemical compound or small peptide. Its druggability to predict docking fitness scoring effectiveness allowing us to generate this drug repurposing screening approach with the primary goal of identifying some actual binders, by combining its cluster free energy ranking output with other chemistry informatics and repositioning In-Silico tools. The usefulness of docking methods for binding mode prediction is well documented. The accuracy of our structural predictions to validate our free energy protocol on these difficult targets have been key on a large scale and in an unbiased fashion to achieve a high level of screening performance. In contrast, the reliability and range of applicability of free energy methods, even when applied to known structures, remains to be fully established (33,48). Therefore, it can be used as an AI-strategy by studying large datasets patterns in complex inverse docking and quantum simulation pipelines. The computational cost of classical geometri be reduced by the approaches which are bas bilistic, randomization and modified geometri probabilistic approach the computational cost thinning out feature points and number of b probabilistic approach of random reduction has been proposed to reduce the computation it decreases retrieval accuracy. The theoretic experimental results of the Monte Carlo algoritization) proposed in (70) suggest that it is possib worst case behavior of the deterministic version and classical geometric hashing, while ensuring probability of a mismatch. In (68,69,70) a modified geo has been proposed to reduce the computatio memory in content-based image retrieval syst similar shape images from the visual database the memory demand, only a subset of image stored in the hash table. The non-uniform distribution of invariants table makes an inefficient storage of the data slow down of the recognition process. The key problem is the selection of a ”good” geometric which can redistribute the data uniformly over All combinations of hash functions have been (70) to choose the best one. In (69), (70) rehash have been suggested. The basic idea is to find a which maps the distribution of invariants to a u bution (33,50,51,60) We envision the Biogeneto-ligandorolTM quantum thinking procedure which can emerge that can be useful to establish advantages and shortcomings as the first step in a ligand parallel and inverse docking and free energy simulation pipeline with an increased success rate of identifying repurposing drugs and herbals with potential anti-COVID-19 biological activities in order to find robust drug combinations for the treatment of the COVID-19 particularly after the virus main protease has developed different enzyme variations. The BiogenetoligandorolTM combined drug combination and drug retargeting pipeline can finish this drug and herbal medicinal plants repurposing virtual screening within 4 to 5 days using a reliable HTS-HVS strategy while suggesting an new era on the surface of the target proteins that are essential in the life cycle of the SARS-COV-2 viruses where potential drug combinations of novel and FDA approved selective inhibitors should bind.

Conclusions

In this study we have found that the Colchicine binds into the pdb:6lu7 SARS-COV-2 proein targets with the docking energies of the (-2.06654, -4.97965, -10.4743, -8.98984, -4.03283, -6.24897, -3.46474, -11.5726, -3.22075, -5.20269) and generates docking energies of the -67,4Kcal/Mol when combined with the Ursolic acid and Remdesivir chemical scaffolds which were generating negative docking energies of the -54,8 Kcal/Mol and -50,8Kcal/Mol respectively when co-targeting with the Colchicine small molecule the same protein targets within the pdb:6lu7 binding cavities. More sprecifically, the two chemical structures of the Remdesivir and Ursolic acid small molecules generated an inhibitory effect against the sequence of the amino acids of the V-M-GLU-166, V-M-LEU-167, V-M-PRO-168, V-M-GLN-189, V-S-PRO-168, V-M-THR-190, V-M-ALA-191, V-M-ALA-2, V-M-VAL-3, V-S-VAL-3, V-M-GLU-166, V-M-LEU-167, V-M-PRO-168, V-S-PRO-168, V-M-GLN-189, V-M-THR-190, V-M-ALA-191, V-M-ALA-2, V-M-VAL-3, V-S-VAL-3 with the the below docking energy values (-400.794, 329.678, -337.184, -907.342, -52.667, -894.194, -194.094, -427.299, -425.681, 0.931221) for the Remdesivir and (-236.408, 0.254828, -101.104, -832.191, -405.854, -74.901, -498.389, 177.232, -269.511, -40.622) for the Ursolic acid chemical strucuture. (68,69,70) The present performs Geometric Hashing-based structural alignment of the putative docking partners on all the library templates, discards solutions with severe steric clashes and, finally, refines the surviving modelled interfaces by allowing side chain and limited backbone flexibility of the interacting proteins while ranking them by global energy by aiming to test and suggest possible drug combinations in order to stop the infection immediately. We created a new track to display the contacts with each of those: Lys711 and Arg355, and SARS-CoV2 PLpro. Interestingly, the Lys711 and Arg355 homo-dimerization site intersects with the Lys711 and Arg355-Remdesivir-Ursolic acid and Colchicine interfaces, suggesting that the combination of the Urtsolic acid, Colchicine and the Remdesivir ligands may also interfere with Lys711 and Arg355 homodimerization. Conversely, the contacts that Lys711 and Arg355 makes with the drug combination of the Remdesivir, Ursolic acid and Colchicine within the SARS-CoV2 PLpro binding sites are distinct from the ones with Remdesivir:The Lys711 and Arg355/-Ursolic acid and Lys711-Remdesivir and Arg355/SARS-CoV2 PLpro –Colcicine interactions may not be affected by other ligands, suggesting an edgetic effect of this drug combination. Our prediction that Remdesivir does not interfere with the Lys711 and Arg355/SARS-CoV2 PLpro interaction is supported by data showing that Lys711 and Arg355 and SARS-CoV2 PLpro co-immunoprecipitate following Remdesivir treatment, which is consistent with Darunavir, Azithromycin and Linoleic acid-stimulated, Lys711 and Arg355-dependant degradation of SARS-CoV2 PLpro (18, 19). Therefore, solutions provided by the BiogenetoligandorolTM cluster of AI-Algorithms in this project indicated to us that the Colchicine, Remdesivir and Ursolic acid drugs are considered to be <<co-administered>> which is something more than important and have to be considered as a first approximation that may require subsequent parallel refinement and docking analysis using more accurate free energy ranking models. by allowing side chain and limited backbone flexibility of the interacting proteins while ranking them by global energy. The method is highly efficient due to the preprocessing of the template library, which were obtained by $d(c) = ||D(q) - D(c)||A$ for the pharmacophoric set of the Remdesivir, Ursolic acid and Colchicine Ci small molecules and the SARS-CoV-2 protein targets into a Geometric Hashing table (TablesS3a,S3b). We anticipate that this Recomborovir drug combination consisted of the combination of the Remdesivir, Ursolic acid and Colchicine small molecules could interact synergistically with the active compounds of the Linoleic acid, Opaganib, Daclatasvir, EIDD-2801, Avigan, Azithromycin but not with the GC376, Minocycline, Baricitimib, Cobicistat, Darunavir, Hydroxychloroquine,and Ritonavir drugs when docked into the SARS-COV2 viruses same protein targets (Tables1a,3b,3c). In conclusion, Biogeneto- ligandorolTM LigandorolTM is very efficientand is not just proposed as an alternative drug repurposing and computational method, but rather as a combined complementary deep learning similarity and quantum mechanics predictive tool to be used in tandem with other In-Silico drug retargeting and computational platforms which could led us to the rational design of novel drug combinations of small molecules and more effective repositioning experimental methods.

- **Availability of data and materials**

The author confirms that the data supporting the findings of this study are available within the article (and/or) its supplementary materials.

- **Competing interests**

No potential competing interest was reported by the author.

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- **Authors' contributions**

Author's diverse contributions to the published work are accurate and agreed.

Author has contributed in the below multiple roles:

- **Conceptualization Ideas, Formulation or evolution of overarching research goals and aims**
- **Methodology, Development and design of methodology; creation of models**
- **Software, Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components**
- **Validation, Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs**
- **Formal analysis Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data**
- **Investigation, Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection**
- **Resources, Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools**
- **Data Curation, Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse**
- **Writing - Original Draft, Preparation, creation and presentation of the published work, specifically writing the initial draft (including substantive translation)**
- **Writing - Review & Editing Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages**
- **Visualization, Preparation, creation and presentation of the published work, specifically visualization/ data presentation**
- **Supervision, Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team**
- **Project administration, Management and coordination responsibility for the research activity planning and execution.**

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- **Significance Statement**

Drug repurposing/repositioning/rescue proposed a computational method to identify potential drug indications by integrating various applications of an existing drug to a new disease indication. In this paper we filtered out residues with relatively small surface accessible areas, and/or with incompatible charge and hydrophobic properties to the ligands of the Remdesivir, Colchicine and Ursolic acid small molecules which could improve the prediction binding free energies or binding orientations of different drug combinations of the Remdesivir, Colchicine and Ursolic acid to treat COVID-19. Finally, an comprehensive web platform by applying AI deep learning models was designed based on our BiogenetoligandorolTM protocol for drug repurposing to significantly reduce user time for data gathering and multi-step analysis without human intervention.In conclusion, BiogenetoligandorolTM -LigandorolTM is not proposed as an alternative drug repurposing method, but rather as a complementary deep learning quantum mechanics tool to be used in tandem with other drug retargeting computational and small molecule repositioning experimental methods.

- **References**

1. Huang YF, Bai C, He F, Xie Y, Zhou H. Review on the potential action mechanisms of Chinese medicines in treating Coronavirus Disease 2019 (COVID-19). Pharmacol Res. 2020;158:104939. doi:10.1016/j.phrs.2020.104939
2. Jimenez-Arellanes A., Meckes M., Torres J., Luna-Herrera J. Anti-mycobacterial triterpenoids from Lantana hispida (Verbenaceae) J. Ethnopharmacol. 2007;111:202–205. doi: 10.1016/j.jep.2006.11.033. (PubMed) (CrossRef) (Google Scholar)
3. Tanachatchairatana T., Bremner J.B., Chokchaisiri R., Suksamrarn A. Antimycobacterial activity of cinnamate-based esters of the triterpenes betulinic, oleanolic and ursolic acids. Chem. Pharm. Bull. 2008;56:194–198. doi: 10.1248/cpb.56.194. (PubMed) (CrossRef) (Google Scholar)
4. López-García S, Castañeda-Sanchez JI, Jiménez-Arellanes A, et al. Macrophage Activation by Ursolic and Oleanolic Acids during Mycobacterial Infection. Molecules. 2015;20(8):14348-14364. Published 2015 Aug 6. doi:10.3390/molecules200814348
5. Gordon CJ, Tchesnokov EP, Feng JY, et al.: The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020, 295:4773-4779.10.1074/jbc.AC120.013056
6. 1. Wang J, Li GL, Ming SL, et al. BRD4 inhibition exerts anti-viral activity through DNA damage-dependent innate immune responses. PLoS Pathog. 2020;16(3):e1008429. Published 2020 Mar 24. doi:10.1371/journal.ppat.1008429.
7. Kraft CS, Hewlett AL, Koepsell S, et al.: The Use of TKM-100802 and Convalescent Plasma in 2 Patients With Ebola Virus Disease in the United States. Clin Infect Dis. 2015, 61:496-502.10.1093/cid/civ334.
8. Rifaioglu AS, Atas H, Martin MJ, et al.: Recent applications of deep learning and machine intelligence on In-Silico drug discovery: methods, tools and databases. Brief Bioinform. 2019, 20:1878-1912. 10.1093/bib/bby061
9. Saha RP, Sharma AR, Singh MK, et al.: Repurposing Drugs, Ongoing Vaccine, and New Therapeutic Development Initiatives Against COVID-19. Front Pharmacol. 2020,11:1258. 10.3389/fphar.2020.01258
10. Shen F., Fu Z.Y., Wu Y.R., Li L., Zhao Y.D., Xia Y., Kuang G.Y. Modernization of Traditional Chinese Medicine and Materia Materia-World Science and Technology. 2020. Based on network pharmacology and high-throughput molecular docking to study the potential molecular mechanism of active compounds tthat bind SARS-Cov-2 specific target protein in Jinhua Qinggan granules to interfere with CovID-19.http://kns.cnki.net/kcms/detail/11.5699.R.20200421.0949.004.html (Google Scholar)
11. Cova, Tânia F G G, Alberto A C C Pais, et al.: Deep Learning for Deep Chemistry: Optimizing the Prediction of Chemical Patterns. Frontiers in chemistry vol. 7 809. 26 Nov. 2019, 10.3389/fchem.2019.00809
12. Tian B, Yang J, Zhao Y, et al. BRD4 Couples NF-κB/RelA with Airway Inflammation and the IRF-RIG-I Amplification Loop in Respiratory Syncytial Virus Infection. J Virol. 2017;91(6):e00007-17. Published 2017 Feb 28. doi:10.1128/JVI.00007-17
13. Yang Z, Papanikolaou S, Reid ACE, et al.: Learning to Predict CrystalPlasticity at the Nanoscale: Deep Residual Networks and Size Effectsin Uniaxial Compression Discrete Dislocation Simulations. Sci Rep.2020, 10:8262-2020. 10.1038/s41598-020-65157-z
14. Karimi M, Wu D, Wang Z, et al.: DeepAffinity: interpretable deep learning of compound-protein affinity through unified recurrent and convolutional neural networks. Bioinformatics. 2019, 35:3329- 3338.10.1093/bioinformatics/btz111
15. Sun X, Ni Y, Zhang M: Rheumotologitsts' view on the use of hydroxyRemdesivir to treat COVID-19. Emerg Microbes Infect. 2020, 9:830-8310.1080/22221751.2020.17601451016/j.resp.2020.103548
16. Mishra SS, Ranjan S, Sharma CS, Singh HP, Kalra S, Kumar N. Computational investigation of potential inhibitors of novel coronavirus 2019 through structure-based virtual screening, molecular dynamics and density functional theory studies (published online ahead of print, 2020 Jul 15). J Biomol Struct Dyn. 2020;1-13. doi:10.1080/07391102.2020.1791957
17. Bochevarov A. D, Harder E, Hughes T. F, Greenwood J. R, Braden D. A, Philipp D. M, Rinaldo D, Halls M. D, Zhang J, & Friesner R. A. (2013). Jaguar: A high-performance quantum chemistry software program with strengths in life and materials sciences.

International Journal of Quantum Chemistry, (18), 2110–2142. 10.1002/qua.24481 (CrossRef) (Google Scholar)
18. Aanouz I, Belhassan A, El-Khatabi K, et al.: Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations (published online ahead of print, 2020 May 6). J Biomol Struct Dyn. 2020, 1-9.10.1080/07391102.2020.1758790
19. Sullivan DJ, Liu Y, Mott BT, Kaludov N, Martinov MN. Discovery of Novel Liver-Stage Antimalarials through Quantum Similarity. PLoS One. 2015;10(5):e0125593. Published 2015 May 7. doi:10.1371/journal.pone.0125593
20. (OCHEM): web platform for data storage, model development and publishing of chemical information. J Comput Aided Mol Des. 2011, 25:533-554. 10.1007/s10822-011-9440-2
21. Walker T, Grulke CM, Pozefsky D, et al.: Chembench: a cheminformatics workbench. Bioinformatics. 2010, 26:3000- 3001.10.1093/bioinformatics/btq556
22. Saha RP, Sharma AR, Singh MK, et al.: Repurposing Drugs, Ongoing Vaccine, and New Therapeutic Development Initiatives Against COVID-19. Front Pharmacol. 2020, 11:1258. 10.3389/fphar.2020.01258
23. Du L, He Y, Zhou Y, et al.: The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar, 7:226-36. 10.1038/nrmicro2090. Epub 2009 Feb 9. PMID: 19198616 PMCID: PMC2750777
24. Gordon CJ, Tchesnokov EP, Feng JY, et al.: The antiviral compound remdesivir potently inhibits RNA- dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020, 295:4773- 4779. 10.1074/jbc.AC120.013056
25. Rifaioglu AS, Atas H, Martin MJ, et al.: Recent applications of deep learning and machine intelligence on In-Silico drug discovery: methods, tools and databases. Brief Bioinform. 2019, 20:1878-1912. 10.1093/bib/bby061
26. Jing Y, Bian Y, Hu Z, et al.: Deep Learning for Drug Design: an Artificial Intelligence Paradigm for Drug Discovery in the Big Data Era (published correction appears in. AAPS J. 2018 Jun, 25:79-2018. 10.1208/s12248-018-0210-0
27. Ma C, Wang L, Xie XQ, et al.: GPU accelerated chemical similarity calculation for compound library comparison. J Chem Inf Model. 2011, 51:1521-1527.10.1021/ci1004948
28. Karimi M, Wu D, Wang Z, et al.: DeepAffinity: interpretable deep learning of compound-protein affinity through unified recurrent and convolutional neural networks. Bioinformatics. 2019, 35:3329- 3338.10.1093/bioinformatics/btz111
29. Balasubramanian K: Mathematical and Computational Techniques for Drug Discovery: Promises and Developments. Curr Top Med Chem. 2018;18(32): 2774-2799.10.2174/1568026619666190208164005. PMID: 30747069
30. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;581(7807):221-224. doi:10.1038/s41586-020-2179-y
31. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. 2020;94(7):e00127-20. Published 2020 Mar 17. doi:10.1128/JVI.00127-20
32. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020;248:117477. doi:10.1016/j.lfs.2020.117477
33. Gallicchio E, Deng N, He P, et al. Virtual screening of integrase inhibitors by large scale binding free energy calculations: the SAMPL4 challenge. J Comput Aided Mol Des. 2014;28(4):475-490. doi:10.1007/s10822-014-9711-9
34. Cavasotto CN, Adler NS, Aucar MG. Quantum Chemical Approaches in Structure-Based Virtual Screening and Lead Optimization. Front Chem. 2018;6:188. Published 2018 May 29. doi:10.3389/fchem.2018.00188
35. Vidler LR, Filippakopoulos P, Fedorov O, et al. Discovery of novel small-molecule inhibitors of BRD4 using structure-based virtual screening. J Med Chem. 2013;56(20):8073-8088. doi:10.1021/jm4011302
36. Perišić, O. Heterodimer binding scaffolds recognition via the analysis of kinetically hot residues. Pharmaceuticals 2018, 11, 29. (Google Scholar) (CrossRef)
37. Haliloglu, T.; Bahar, I.; Erman, B. Gaussian Dynamics of Folded Proteins. PRL 1997, 79, 3090– 3093. (Google Scholar) (CrossRef)
38. Bahar, I.; Atilgan, A.R.; Erman, B. Direct evaluation of thermal fluctuations in proteins using a single- parameter harmonic potential. Fold. Des. 1997, 2, 173–181. (Google Scholar) (CrossRef)

39. Náray-Szabó G, Oláh J, Krámos B. Quantum mechanical modeling: a tool for the understanding of enzyme reactions. Biomolecules. 2013;3(3):662-702. Published 2013 Sep 23. doi:10.3390/biom3030662
40. Demirel, M.C.; Atiligan, A.R.; Jernigan, R.L.; Erman, B.; Bahar, I. Identification of kinetically hot residues in proteins. Protein Sci. 1998, 7, 2522–2532. (Google Scholar) (CrossRef)
41. Bahar, I.; Erman, B.; Jernigan, R.L.; Atilgan, A.R.; Covell, D.G. Collective motions in HIV-1 reverse transcriptase: Examination of flexibility and enzyme function. J. Mol. Biol. 1999, 285, 1023–1037. (Google Scholar) (CrossRef)
42. Yang, L.; Eyal, E.; Chennubhotla, C.; Jee, J.; Gronenborn, A.M.; Bahar, I. Insights into Equilibrium Dynamics of Proteins from Comparison of NMR and X-Ray Data with Computational Predictions. Structure 2007, 15, 741–749. (Google Scholar) (CrossRef) (PubMed)
43. Haliloglu, T.; Keskin, O.; Ma, B.; Nussinov, R. How Similar Are Protein Folding and Protein Binding Nuclei? Examination of Vibrational Motions of Energy Hot Spots and Conserved Residues. Biophys. J. 2005, 88, 1552–1559. (Google Scholar) (CrossRef) (PubMed)
44. Bogan, A.A.; Thorn, K.S. Anatomy of hot spots in protein interfaces. J. Mol. Biol. 1998, 280, 1–9. (Google Scholar) (CrossRef)
45. Moreira, I.S.; Fernandes, P.A.; Ramos, M.J. Hot spots-A review of the protein-protein interface determinant amino-acid residues. Proteins Struct. Funct. Bioinform. 2007, 68, 803–812. (Google Scholar) (CrossRef)
46. Tuncbag, N.; Gursoy, A.; Keskin, O. Identification of computational hot spots in protein interfaces: Combining solvent accessibility and inter-residue potentials improves the accuracy. Bioinformatics 2009, 25, 1513–1520. (Google Scholar) (CrossRef)
47. Hu Z, Hung JH, Wang Y, Chang YC, Huang CL, Huyck M, DeLisi C. VisANT 3.5: multi-scale network visualization, analysis and inference based on the gene ontology. Nucleic Acids Res. 2009 Jul;37(Web Server issue):W115-21. doi: 10.1093/nar/gkp406. Epub 2009 May 21. PMID: 19465394; PMCID: PMC2703932.
48. Barbault F, Maurel F. Simulation with quantum mechanics/molecular mechanics for drug discovery. Expert Opin Drug Discov. 2015 Oct;10(10):1047-57. doi: 10.1517/17460441.2015.1076389. Epub 2015 Aug 8. PMID: 26289577.
49. Lise, S.; Buchan, D.; Pontil, M.; Jones, D.T. Predictions of Hot Spot Residues at Protein-Protein Interfaces Using Support Vector Machines. PLoS ONE 2011, 6, e16774. (Google Scholar) (CrossRef) (PubMed)
50. Kozakov, D.; Hall, D.R.; Chuang, G.; Cencic, R.; Brenke, R.; Grove, L.E.; Beglov, D.; Pelletier, J.; Whitty, A.; Vajda, S. Structural conservation of druggable hot spots in protein-protein interfaces. Proc. Natl. Acad. Sci. USA 2011, 108, 13528–13533. (Google Scholar) (CrossRef) (PubMed)
51. Jin Z, Du X, Xu Y, et al. : Structure-based drug design, virtual screening and high-throughput screening rapidly identify antiviral leads targeting COVID-19. bioRxiv. 2020. 10.1101/2020.02.26.964882 (CrossRef) (Google Scholar)
52. Ju J, Kumara S, Li X, et al. : Nucleotide analogues as inhibitors of viral polymerases. bioRxiv. 2020. 10.1101/2020.01.30.927574 (CrossRef) (Google Scholar)
53. Lin CW, Tsai FJ, Tsai CH, et al. : Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res. 2005;68(1):36–42. 10.1016/j.antiviral.2005.07.002 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
54. Pillaiyar T, Manickam M, Namasivayam V, et al. : An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem. 2016;59(14):6595–6628. 10.1021/acs.jmedchem.5b01461 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
55. Kuo CJ, Liang PH: Characterization and inhibition of the main protease of severe acute respiratory syndrome coronavirus. ChemBioEng Reviews. 2015;2:118–132. 10.1002/cben.201400031 (CrossRef) (Google Scholar)
56. Chu CM, Cheng VC, Hung IF, et al. : Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252–256. 10.1136/thorax.2003.012658 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
57. Stockman LJ, Bellamy R, Garner P: SARS: systematic review of treatment effects. PLoS Med. 2006;3(9):e343. 10.1371/journal.pmed.0030343 (PMC free article) (PubMed) (CrossRef) (Google Scholar)

58. Gruber C, Steinkellner G: Coronavirus COVID-19 (formerly known as Wuhan coronavirus and 2019-nCoV) - what we can find out on a structural bioinformatics level. 2020. Reference Source (Google Scholar)
59. Dayer MR, Taleb-Gassabi S, Dayer MS: Lopinavir; a potent drug against coronavirus infection: insight from molecular docking study. Arch Clin Infect Dis. 2017;12(4):e13823 10.5812/archcid.13823 (CrossRef) (Google Scholar)
60. Nukoolkarn V, Lee VS, Malaisree M, et al. : Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL pro inhibitors. J Theor Biol. 2008;254(4):861–867. 10.1016/j.jtbi.2008.07.030 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
61. Zhang XW, Yap YL: Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. Bioorg Med Chem. 2004;12(10):2517–2521. 10.1016/j.bmc.2004.03.035 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
62. Wu CY, Jan JT, Ma SH, et al. : Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A. 2004;101(27):10012–10017. 10.1073/pnas.0403596101 (PMC free article) (PubMed) (CrossRef) (Google Scholar)
63. Alberca Lucas N., Chuguransky Sara R., Álvarez Cora L., Talevi Alan, Salas-Sarduy Emir, In silico Guided Drug Repurposing: Discovery of New Competitive and Non-competitive Inhibitors of Falcipain-2, Frontiers in Chemistry, 7, 2019, 534, https://www.frontiersin.org/article/10.3389/fchem.2019.00534, DOI=10.3389/fchem.2019.00534, ISSN=2296-2646,
64. Irene Maffucci and Alessandro Contini., In Silico Drug Repurposing for SARS-CoV-2 Main Proteinase and Spike Proteins, Journal of Proteome Research 2020 19 (11), 4637-4648. DOI: 10.1021/acs.jproteome.0c00383
65. Arun KG, Sharanya CS, Abhithaj J, Francis D, Sadasivan C. Drug repurposing against SARS-CoV-2 using E-pharmacophore based virtual screening, molecular docking and molecular dynamics with main protease as the target (published online ahead of print, 2020 Jun 22). J Biomol Struct Dyn. 2020;1-12. doi:10.1080/07391102.2020.1779819
66. Nobuaki Yasuo and Masakazu Sekijima., Improved Method of Structure-Based Virtual Screening via Interaction-Energy-Based Learning. Journal of Chemical Information and Modeling 2019 59 (3), 1050-1061. DOI: 10.1021/acs.jcim.8b00673
67. Phatak SS, Zhang S. A novel multi-modal drug repurposing approach for identification of potent ACK1 inhibitors. Pac Symp Biocomput. 2013;29-40.
68. Estrin M, Wolfson HJ. SnapDock-template-based docking by Geometric Hashing. Bioinformatics. 2017;33(14):i30-i36. doi:10.1093/bioinformatics/btx233
69. Lamdan Y., Wolfson H.J. (1988). Geometric hashing: a general and efficient model-based recognition scheme. In Proceedings of the 2nd International Conference on Computer Vision, IEEE Computer Society, pp. 238–249.
70. Jayaraman, Umarani & Gupta, Amit & Prakash, Surya & Gupta, Phalguni. (2011). An Enhanced Geometric Hashing. IEEE International Conference on Communications. 1-5. 10.1109/icc.2011.5962658.