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ORIGINAL ARTICLE

Comparative docking studies of drugs and phytocompounds for emerging variants of SARS-CoV-2

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Abstract

In the last three years, COVID-19 has impacted the world with back-to-back waves leading to devastating consequences. SARS-CoV-2, the causative agent of COVID-19, was first detected in 2019 and since then has spread to 228 countries. Even though the primary focus of research groups was diverted to fight against COVID-19, yet no dedicated drug has been developed to combat the emergent life-threatening medical conditions. In this study, 35 phytocompounds and 43 drugs were investigated for comparative docking analysis. Molecular docking and virtual screening were performed against SARS-CoV-2 spike glycoprotein of 13 variants using AutoDock Vina tool 1.5.6 and Discovery Studio, respectively, to identify the most efficient drugs. Selection of the most suitable compounds with the best binding affinity was done after screening for toxicity, ADME (absorption, distribution, metabolism and excretion) properties and drug-likeliness. The potential candidates were discovered to be Liquiritin (binding affinities ranging between −7.0 and −8.1 kcal/mol for the 13 variants) and Apigenin (binding affinities ranging between −6.8 and −7.3 kcal/mol for the 13 variants) based on their toxicity and consistent binding affinity with the Spike protein of all variants. The stability of the protein–ligand complex was determined using Molecular dynamics (MD) simulation of Apigenin with the Delta plus variant of SARS-CoV-2. Furthermore, Liquiritin and Apigenin were also found to be less toxic than the presently used drugs and showed promising results based on in silico studies, though, confirmation using in vitro studies is required. This in-depth comparative investigation suggests potential drug candidates to fight against SARS-CoV-2 variants.

Keywords COVID-19 · Variants · Drug repurposing · Docking · Phytocompounds · MD Simulation

Abbreviations

ADMET	Absorption, distribution, metabolism, excretion, and toxicity
ATB	Automated topology builder
COVID 19	Coronavirus disease
LD50	Lethal dose 50
MD SIMULATION	Molecular dynamics simulation
MERS	Middle East respiratory syndrome coronavirus
MMBPSA	Molecular Mechanics Poisson-Boltzmann surface area
NCBI	National Center of Biotechnology Information
PDB	Protein data bank
PROTOX II	Prediction of toxicity of chemicals

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ROG	Radius of gyration
RMSD	Root mean square deviation
RMSF	Root mean square fluctuations
SARS- CoV -2	Severe Acute Respiratory Syndrome Coronavirus 2
SASA	Solvent accessible surface area
VOC	Variant of concern
VOI	Variant of interest

Introduction

It is not unusual that a *Coronaviridae* virus has infected humans. In 2002–03, there was a Severe Acute Respiratory Syndrome (SARS) outbreak, followed by that, in 2012 the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged and affected the Middle Eastern countries (Rabaan et al. 2020). The tremendous evolutionary adaptability of coronaviruses to the environment and host specificity eventually gave rise to SARS-CoV-2, which has been inflicting chaos in the world with a series of new mutations (Zheng 2020). COVID-19 has surfed successive waves in the preceding two years, with new variants surfacing one after the other, leaving the infection vulnerable to rumours because of its poor understanding (Maher et al. 2021). According to the World Health Organisation, there have been a total of 5 Variants of Concern (VOCs), namely Alpha, Beta, Gamma, Delta and Omicron (Chugh et al. 2022).

Owing to the mutability of this virus, many variants of SARS-CoV-2 have originated and have been more infectious and transmissible than before. Therefore, one of the major obstacles in controlling the Pandemic has been the absence of an efficient therapeutic strategy against the existing and emerging variants (Aleem et al. 2022).

Computational biology has been proved to be a crucial tool in indicating the potential phytocompounds from medicinal plants and repurposed pharmaceuticals in the fight against SARS-CoV-2 (Scherman and Fetro 2020; Toor et al. 2021). Within the initial few months of the COVID-19 pandemic, there was a rise in clinical trials of repurposing drugs such as Hydroxychloroquine, Remdesivir, Ritonavir, Lopinavir, Ivermectin, Interferon and several other immunomodulators and anti-inflammatory drugs. However, most of them either had serious side effects or did not seem to affect the virus significantly (Toor et al. 2021; Hall and Ji 2020; Khanna et al. 2021; Martinez 2021; Yadav et al. 2021). In parallel, research into herbal cures (phytocompounds) also grew rapidly due to their minimal adverse effects and widespread acceptance (Basu et al. 2020; Pk et al. 2020). Furthermore, the use of plant extracts in traditional medicine and novel drugs have been productive multiple times over the past few centuries (Hakobyan et al. 2016; Rolta et al. 2021).

With the growing number of new variants, it has become necessary to analyse the differential effects of the available therapeutics and to assess their efficacy on each variant of SARS-CoV-2. Therefore, a rapid and cost effective in silico method to identify existing molecules or phytocompounds could help in building a repository for clinical trials. Moreover, it would decrease the time for discovery of new drug candidates and may provide significant help for drug development that can be interpreted into clinical applications to combat SARS-CoV-2 (Dotolo et al. 2021; Rudrapal and J. Khairnar S et al. 2020).

In this study, various drugs and phytocompounds have been selected for molecular docking with Spike glycoprotein, a trimeric club shaped structural protein of the SARS-CoV-2 virus, which facilitates viral fusion with the host cell (Chugh et al. 2022). As Spike gene has a nucleotide mutation rate of 8.066×10^{-4} substitutions per site per year, while the SARS-CoV-2 genome has a rate of 6.677×10^{-4} substitutions per site per year, so certain mutations, particularly in the Spike glycoprotein, have been believed to enhance viral infectivity and transmissibility, resulting in emergence of several variants classified as Variants of Concern (VOC) and Variants of Interest (VOI) by the World Health Organization (Hu et al. 2021; Wang et al. 2020; Singh et al. 2021a, b, c, d). Hence, in this comparative study, molecular docking was performed with Spike glycoprotein from 13 variants of SARS-CoV-2. This may prove to be beneficial in curing COVID-19 as the best phytocompound and drug, effective on all the variants have been compared and analysed using in silico studies.

Materials and methods

Ligand preparation

Based on previous studies on RNA viruses, 43 drugs and 35 phytocompounds were selected for virtual screening and molecular docking study against SARS-CoV-2 Spike glycoprotein (Toor et al. 2021; Hall and Ji 2020; Khanna et al. 2021; Poratti and Marzaro 2019). The 3-dimensional structures of all the ligands were retrieved from DrugBank (https://go.drugbank.com/k) and PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Further, the files were converted into protein data bank (PDB) format using OpenBabel and all the selected ligands were prepared using AutoDock Vina 1.5.6 tools. Table 1 shows the selected 78 drugs and phytocompounds (see Table 2).

Retrieval of Spike sequences of SARS-CoV-2 variants

The crystal structures of Spike glycoprotein region for 4 different SARS-CoV-2 variants were downloaded from the

Table 1 List of 46 drugs and 36 phytocompounds

S. No	Drugs	Phytocompounds
1	*N*-acetylcysteine	Emodin
2	2-mercaptoethane sulfonate, sodium salt (MESNA)	Thymol
3	Tiopronin	Carvacrol
4	Cysteamine	Artemisinin
5	Amifostine (parent drug) WR-1065 (active metabolite)	Aloe-emodin
6	Erdosteine (parent drug) Met I (active metabolite)	Anthrarufin
7	Penicillamine	Alizarine
8	Glutathione	Dantron
9	Cangrelor	1,8 dihydroxy-3-carboxyl-9,10-anthraquinone or rhein
10	Dpnh (NADH)	Cucurbitacin B (−112.09)
11	Flavin adenine dinucleotide (FAD) adeflavin	Cardiofoliolide (−111.5)
12	Iomeprol	Apigenin (−98.84)
13	Coenzyme A	Pyrethrin (−92.98)
14	Tiludronate	Zingiberene
15	Flavin adenine dinucleotide (FAD) adeflavin	Vasicine
16	Azithromycin	Andrographolide
17	Remdesivir	Carvacol
18	Peramivir	Costunolide
19	Abacavir	Eugenol
20	Didanosine	Pyrethrin
21	Tenofovir	Chalcone
22	Colistin	6-Shogaol
23	Eugenol	Myristicin
24	Liquiritin	Bis (3, 5, 5-trimethylhexyl) phthalate
25	Emblicanin A	Tangeretin
26	3-Carene	Nelfinavir
27	Allicin	Griffithsin
28	Glycyrrhizic acid	Kamferol
29	Nafamostat	Curcumin
30	Oseltamivir	Pterostilbene
31	Telbivudine	Fisetin
32	Zanamavir	Quercetin
33	Stavudine	Isorhamnetin
34	Raltegravir	Genistein
35	Zalcitabine	Luteolin
36	Favipiravir	Resveratrol
37	Ribavirin	–
38	Galidesivir	–
39	Lopinavir	–
40	Ritonavir	–
41	Azadirachtin	–
42	Camostat	–
43	Doxycycline	–
44	Ivermectin	–
45	abemaciclib	–
46	2-deoxy- Glucose	–

(Source: elaborated in Table S3)

Table 2 Summary of SARS-CoV-2 variants

WHO label	Pango Lineage	Emergence	Spike mutation		
			RBD region mutations	Other S1and S2 mutations	Furin
Alpha	B.1.1.7	UK, Sep 2020	N501Y	DelH69, DelV70, ΔY144, A570D, D614G, T716I, S982A, D1118H	P681H
Beta	B.1.351	South Africa, May-2020	K417N, E484K, N501Y	L18F, D80A, D215G, ΔL242, ΔA243, ΔL244, R246I, D614G, A701V	N/A
Gamma	P.1	Brazil, Nov-2020	K417T, E484K, N501Y	L18F, T20N, P26S, D138Y, R190S, D614G, H655Y, T1027I, V1176F	N/A
Delta	B.1.617.2	India, Oct-2020	L452R, **T478K,**	G142D, D614G, T**19R, 156del, 157del, R158G, D950N**	P681R
Epsilon	B.1.427/B.1.429	United States of America, Mar-2020	L452R	S13I, W152C, D614G	N/A
Zeta	P.2	Brazil, Apr-2020	E484K	D614G, F656, V1176F, T859I	N/A
Eta	B.1.525	Multiple countries, Dec-2020	E484K	O52R, Q677H, F888L, D614G, A67V	N/A
Theta	P.3	Philippines, Jan-2021	E484K, N501Y	D614G, E1092K, H1101Y, V1176F	P681H
Iota	B.1.526	United States of America, Nov-2020	E484K, S447N	L5F, T95I, D253G, D614G, A701V	N/A
Kappa	B.1.617.1	India, Oct-2020	E484Q, L452R,	G142D, D614G, T95I, E154K, Q1071H, M153I	P681R

(Source: https://viralzone.expasy.org/9556, https://cov-lineages.org/)

protein data bank (Wild Type (6VYB) (Walls et al. 2020), Alpha (7LWT) (Gobeil et al. 2021), Beta (7LYQ) (Gobeil et al. 2021), Omicron (7QO7) (Ni et al. 2021)) (https://www.rcsb.org/). Remaining 9 were modelled using Swiss Model based on their amino acid sequences in FASTA format (Gamma (MW642248), Delta (QWO57033), Zeta (QVE55301.1), Iota (QTP80309.1), Theta (QVR41797.1), Epsilon (QPJ72086.1), Eta (QWO17721.1), Kappa (QTY54081.1), Delta Plus (QWS06686.1)), retrieved from NCBI (National Center for Biotechnology Information) virus (https://www.ncbi.nlm.nih.gov/). The information about all the selected variants and their mutations is summarized in Supplementary Table 2 and Table S1, respectively. The Ramachandran plots of the strains are shown in Supplementary Fig. S1.

Target protein preparation

The AutoDock Vina tool 1.5.6 was used for preparation of the protein structures. The binding site for protein–ligand interaction of the target Spike protein from different variants were determined through grid box generation by adjusting the grid parameter x, y, z coordinates value. The grid values of all the 13 variants are provided in Supplementary Table S2.

Virtual screening and molecular docking

Molecular docking study of the selected ligands (43 drugs and 35 phytocompounds) against Spike protein of 13 variants was done using AutoDock Vina tool 1.5.6, following the protocol described by Verma et al. (Verma et al. 2021). After the completion of the docking search, the best conformation with the lowest docked energy was chosen and the protein–ligand complex was analyzed using Discovery Studio (https://discover.3ds.com/d) to examine the list of interactions within the complex. Following that, the suitable compounds were selected for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis.

ADMET prediction of drugs and phytocompounds

ADMET screening was done to determine the absorption, toxicity, and drug-likeliness properties of ligands (Dong et al. 2018). The 3D structures of ligands were uploaded on SWISSADME (Molecular Modeling Group of the Swiss Institute of Bioinformatics), Molinspiration cheminformatics (a spin-off of Bratislava University), and ProTox-II (Prediction of TOXicity of chemicals) web servers (Charite University of Medicine, Institute for Physiology, Structural Bioinformatics Group, Berlin, Germany) for ADMET screening. ProTox-II web server was used to predict toxicity profile of the chemical (http://tox.charite.de/protox_II) (Singh et al. 2021a, b, c, d; Banerjee et al. 2018). The toxicity of a ligand is measured in terms of toxicity endpoints such as mutagenicity, carcinogenicity, etc. It can also be measured both quantitatively such as LD50 (lethal dose) values, where Class I ($LD50 \leq 5$) and II ($5 < LD50 \leq 50$) are considered fatal if swallowed and Class VI ($LD50 > 5000$) is non-toxic, and qualitatively, such as binary (active or inactive) for certain cell types and assays or indication area such as cytotoxicity, immunotoxicity and hepatotoxicity (Parasuraman 2011).

Molecular descriptors and drug likeliness properties of compounds were analyzed using the tool Molinspiration

server (http://www.molinspiration.com), based on Lipinski's Rules of five (Frey and Bird 2011).

Molecular dynamics simulation

MD simulation was done with GROMACS 2018.3 (simulation in duplicate) (Abraham et al. 2015) software which was installed in ubuntu 18.04 LTS, to study the stability of protein–ligand complexes over the period of 100 ns. Docked structures of the protein–ligand complexes (Apigenin with Delta plus Variant) were used in the simulation study. The target protein was processed and the topology file was prepared using pdb2gmx and GROMOS54a7_atb. Force field was downloaded from the automated topology builder website and incorporated into GROMACS. The ligand topology file was prepared using the automated topology builder (ATB) version 3.0. The solvent addition was done in a cubic box using a box distance 1.0 nm from closest atom in the protein. To neutralise the device, the Cl- ions calculated from the genion module for each protein were used. The energy was minimised using the steepest descent algorithm with 50,000 steps and a cumulative force of 5 kJ mol^{-1}, as well as the Verlet cut-off scheme with Particle Mesh Ewald (PME) columbic interactions. During the equilibration process, position restraints were used. Following that, NVT equilibration was performed at 300 K with 100 ps in 50,000 steps, using the leapfrog integrator and NPT equilibration was performed with Parrinello-Rahman (pressure coupling), 1 bar reference pressure, and 100 ps in 50,000 steps. The LINCS algorithm was used to constrain the length of all bonds. For long-range electrostatics, the Particle-mesh Ewald (PME) algorithm was used. The protein–ligand complex's MD was run for 100 ns (in duplicate). Following efficient completion of Molecular dynamic simulation, the root mean square deviation (RMSD) of backbone residues, the number of hydrogen bonds, root mean square fluctuations (RMSF), Radius of gyration (ROG) & Solvent accessible surface area (SASA) were calculated (Verma et al. 2021; Darden et al. 1999; Hess et al. 1997; Páll et al. 2015).

Estimation of free energy of binding

The free energy of binding calculation was done using the standalone program, G-MMPBSA (Rolta et al. 2021; Egan et al. 2000; Kumari and Kumar 2014; Kushwaha and Kaur 2021; Pant et al. 2020) based on the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method. The average binding energy calculations were done by a python script provided in G-MMPBSA program.

Results

Molecular docking of drugs and phytocompounds with different variants of SARS-CoV-2

A total of 35 phytocompounds and 43 drugs were used for molecular docking with the Spike protein of all 13 SARS-CoV-2 variants (Table 1). On the basis of their binding affinities with all the variants, 10 drugs were chosen, namely Dpnh (NADH), Flavin Adenine Dinucleotide (FAD) Adeflavin, Liquiritin, Glycyrrhizic acid, Raltegravir, Ritonavir, Doxycycline, Ivermectin, Abemaciclib and Nafamostat (Table 3), out of which Liquiritin showed comparable affinities with all the 13 variants (between -7.0 and -8.1 kcal/mol). Similarly, 15 phytocompounds were chosen, namely, Emodin, Artemisinin, Aloe-emodin, Anthrarufin, Alizarine, Dantron, Rhein, Cucurbitacin B, Apigenin, Curcumin,

Table 3 Docking score of drugs with 13 variants of SARS-CoV-2

Drugs	Binding energy (kcal/mol)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Dpnh (NADH)	− 8.3	− 7.3	− 8.2	− 9	− 8.5	− 8.3	− 9	− 9	− 8.7	− 9	− 8.3	− 8.5	− 7.4
Flavin adenine dinucleotide (fad) adeflavin	− 8.5	− 8.8	− 8.4	− 9	− 8.4	− 9.3	− 8.9	− 8.3	− 9.1	− 9.5	− 8.5	− 8.9	− 7.0
Liquiritin	− 7.5	− 7.2	− 7	− 7.7	− 7.7	− 8	− 7.4	− 7.3	− 7.5	− 8.1	− 7.3	− 7.3	− 7.2
Glycyrrhizic acid	− 7.5	− 7.3	− 6.9	− 7.6	− 7.3	− 8.1	− 7.6	− 7.8	− 7.5	− 8	− 7.5	− 7.8	− 9.2
Raltegravir	− 7.6	− 6.7	− 7.2	− 7.6	− 7.3	− 8	− 7.5	− 7.3	− 7.4	− 8	− 7.3	− 7.4	− 7.9
Ritonavir	− 8.2	− 7	− 6.5	− 8.2	− 8	− 7.8	− 8.2	− 8.2	− 7.9	− 7.6	− 6.5	− 8.4	− 7.5
Doxycycline	− 8.1	− 7.5	− 8.1	− 8.2	− 8.2	− 8.5	− 8.1	− 8.2	− 8.2	− 8.6	− 8.2	− 8.2	− 7.5
Ivermectin	− 10.4	− 9.7	− 9.5	− 10.2	− 10.2	− 9.7	− 10.2	− 10.2	− 10.2	− 9.8	− 10.3	− 10	− 9.6
Abemaciclib	− 7.7	− 7.2	− 7.4	− 7.8	− 7.7	− 7.6	− 7.8	− 7.6	− 7.7	− 7.6	− 7.6	− 7.6	− 7.1
Nafamostat	− 7.4	− 6.8	− 7.5	− 7.8	− 7.2	− 7.7	− 7.6	− 7.7	− 7.6	− 7.5	− 7.6	− 6.8	− 7.1

1 Wuhan (Wild type), 2 Alpha, 3 Beta, 4 Eta, 5 Zeta, 6 Theta, 7 Gamma, 8 Delta, 9 Epsilon, 10 Iota, 11 Kappa, 12 Delta Plus, 13 Omicron

Fisetin, Quercetin, Isorhamnetin, Genistein and Luteolin (Table 4), out of which Apigenin showed similar binding affinities for all variants (between −6.8 and −7.3 kcal/mol). List of chosen drugs and phytocompounds with their respective Accession Numbers/Pubchem ID is summarized in supplementary Table S3.

The binding affinity of all 35 phytocompounds and 43 drugs along with their interacting amino acids were visualised using Discovery Studio as mentioned in supplementary Table S4.

Toxicity prediction of drugs and phytocompounds

The 10 drugs and 15 phytocompounds were analysed by Molinspiration, Protox II and SWISSADME to check for Lipinski's rule, toxicity and ADME respectively. ADME data showed that most of the selected drugs were water-soluble, but only a few had significant GI absorption as shown in Table 5. In the case of phytocompounds, all of them showed good water solubility and high GI absorption except Cucurbitacin B (Table 5).

Toxicity data generated using the Protox II online server showed that among all the drugs, Ivermectin and Raltegravir are Class II and III drugs respectively, while the other drugs belong to Class IV–VI. As for phytocompounds, Cucurbitacin B is a Class II drug, Fisetin and Quercetin are Class III drugs, and the others are categorised as Class IV-VI drugs. Also, Apigenin and Genistein are both non-toxic and each has an LD50 value of 2500. Toxicity data of drugs and phytocompounds are summarised in Table 6. Drug likeliness estimation of active drugs and phytocompounds was done by Molinspiration online server. According to, *in-silico* drug-likeliness prediction Liquiritin showed zero violoations; while Raltegravir, Doxycycline, Nafamostat, Abemaciclib, were found to violate only one of the rules making them suitable candidates for further analysis. On the contrary, in phytocompounds only Cucurbitacin B showed 1 violation, whereas the other phytocompounds followed all rules of drug-likeliness data as summarised in Table 7.

Based on our comparative study, Liquiritin (between −7.0 to −8.1 kcal/mol) and Apigenin (between −6.8 and −7.3 kcal/mol) passed the toxicity prediction, drug likeliness and also have a consistent binding affinity to each of the the 13 variants (Tables 3, 4).

Liquiritin showed hydrogen bonding with Thr300, Ser50, Asn315, Arg317, Gln626 and hydrophobic interactions with Cys299, Ala290, Cys289, Glu296, Lys302, Thr628, Thr272, Ser314, Trp631, Gln319 in Delta variant; and in case of Delta plus variant it makes hydrogen bonds with Gln626, Leu627, Ser314, Thr300, Thr272, Ser50 and hydrophobic interactions with Arg271, Cys299, Ala290, Thr272, Thr628, Pro629, Glu296, Lys302, Cys289. Similarly, Apigenin made hydrogen bonds with Arg1012 and hydrophobic interaction with Thr959, Ala956, Tyr1005, Leu960, Ser1001, Gln963, Thr1004, Gln1008, Gln952, Gln955 in delta strains in case of delta plus apigenin showed only hydrophobic interactions with Thr 959, Gln 1008, Gln 952, Gln 955, Ala 956, Arg 1012, Tyr 1005, Leu 960, Ser 1001, Gln 963, Thr 1004 amino acids the most important variants, are summarized in Table 8 and Figs. 1, 2,3 and 4.

Table 4 Docking score of phytocompounds with 13 variants of SARS-CoV-2

Phytocompounds	Binding Energy (kcal/mol)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Emodin	− 7.2	− 6.1	− 7.1	− 6.7	− 6.3	− 6.9	− 6.8	− 6.6	− 6.7	− 6.8	− 6.3	− 6.6	− 6.6
Artemisinin	− 6.9	− 5.9	− 6.9	− 7.0	− 7	− 7.5	− 7.4	− 7	− 7.4	− 7.5	− 7.1	− 7.2	− 7.6
Aloe-emodin	− 7.1	− 6.3	− 7	− 7.0	− 6.8	− 6.6	− 6.9	− 6.9	− 6.8	− 6.7	− 6.9	− 6.8	− 7.4
Anthrarufin	− 7	− 6.6	− 7.1	− 7.5	− 7.5	− 6.9	− 7.2	− 7.5	− 7.3	− 6.8	− 7.5	− 7.4	− 7.0
Alizarine	− 7.3	− 6.5	− 7.3	− 7.6	− 6.9	− 7.2	− 7.4	− 7.6	− 7.4	− 7.1	− 7.6	− 7.5	− 6.8
Dantron	− 6.8	− 6.9	− 7.1	− 6.9	− 6.8	− 6.5	− 6.7	− 6.8	− 6.8	− 6.4	− 6.9	− 6.8	− 7.5
Rhein	− 7.2	− 6.5	− 7.3	− 7	− 7.2	− 7	− 7	− 7.2	− 7	− 7.0	− 7.2	− 7.1	− 7.5
Cucurbitacin B	− 7.1	− 6.3	− 6.8	− 8.3	− 7.3	− 7.8	− 8.2	− 8.2	− 8.2	− 7.9	− 7.3	− 8.3	− 7.6
Apigenin	− 7.1	− 6.8	− 7.1	− 7.0	− 7	− 7	− 7.2	− 7	− 7.2	− 7.0	− 7.0	− 7.1	− 7.3
Curcumin	− 6.6	− 6.5	− 6.9	− 6.7	− 6.3	− 6.5	− 6	− 6.6	− 6.7	− 6.4	− 6.3	− 6.7	− 6.1
Fisetin	− 7.2	− 6.6	− 7.5	− 6.9	− 6.8	− 7.1	− 6.8	− 6.8	− 7.4	− 7.2	− 6.8	− 6.8	− 6.7
Quercetin	− 7	− 7.1	− 7.2	− 7.0	− 6.9	− 7.1	− 7	− 7	− 7	− 7.3	− 7.0	− 7.0	− 7.0
Isorhamnetin	− 6.7	− 6.4	− 7	− 6.9	− 6.5	− 6.8	− 7	− 6.9	− 7	− 6.6	− 6.3	− 6.9	− 7.1
Genistein	− 6.8	− 6.5	− 7.3	− 6.8	− 6.8	− 7.1	− 6.7	− 6.7	− 6.8	− 7.1	− 6.8	− 6.8	− 7.2
Luteolin	− 7.1	− 6.8	− 7.4	− 7.2	− 7.1	− 7.1	− 7.4	− 7.2	− 7.4	− 7.2	− 7.1	− 7.3	− 7.3

1 Wuhan (Wild type), 2- Alpha, 3- Beta, 4- Eta, 5- Zeta, 6- Theta, 7- Gamma, 8- Delta, 9-Epsilon, 10-Iota, 11- Kappa, 12- Delta Plus, 13- Omicron

Table 5 ADME prediction of drugs and phytocompounds by swiss ADME server

	SwissADME								
	Consensus log PO/W	Water solubility	GI absorption	TPSA (Å2)	Lipinski's rule	Ghose rule	Veber rule	Egan rule	Muegge rule
Name of compounds									
Dpnh (NADH)	− 4.19	Highly soluble	Low	337.24 $Å^2$	No; 3 violations	No; 4 violations	No; 2 violations	No; 1 violation	No; 5 violations
Flavin Adenine Dinucleotide (FAD) Adeflavin	− 2.89	Very soluble	Low	382.55 $Å^2$	No; 3 violations	No; 4 violations	No; 2 violations	No; 1 violation	No; 5 violations:
Liquiritin	0.34	Soluble	Low	145.91 $Å^2$	Yes; 0 violation	Yes	No; 1 violation	No; 1 violation	Yes
Glycyrrhizic acid	1.49	Poorly soluble	Low	267.04 $Å^2$	No; 3 violations	No; 3 violations	No; 1 violation	No; 1 violation	No; 4 violations
Raltegravir	1.38	Soluble	Low	152.24 $Å^2$	Yes; 1 violation	Yes	No; 1 violation	No; 1 violation	No; 1 violation
Ritonavir	5.03	Poorly soluble	Low	202.26 $Å^2$	No; 2 violations	No	No	No	No
Doxycycline	− 0.34	Soluble	Low	181.62 $Å^2$	Yes; 1 violation	Yes	No	No	No
Ivermectin	6.68	Insoluble	Low	340.12 $Å^2$	No; 3 violations	No	No	No	No
Nafamostat	2.16	Soluble	High	138.07 $Å^2$	Yes; 0 violation	Yes	Yes	No; 1 violation	Yes
Abemaciclib	4.04	Moderately soluble	High	75.00 $Å^2$	Yes; 1 violation	No; 2 violations	Yes	Yes	Yes
Name of Phytocompounds									
Emodin	1.87	Soluble	High	94.83 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Artemisinin	2.49	Soluble	High	53.99 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Aloe-emodin	1.5	Soluble	High	94.83 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Anthrarufin	2.16	Moderately soluble	High	74.60 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Alizarine	2.02	Soluble	High	74.60 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Dantron	2.04	Soluble	High	74.60 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
1,8 dihydroxy-3-carboxyl-9,10-anthraquinone or rhein	1.47	Soluble	High	111.90 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Cucurbitacin B (-112.09)	3.17	Moderately soluble	Low	138.20 $Å^2$	Yes; 1 violation:	No; 3 violations	Yes	No; 1 violation:	Yes
Apigenin	2.11	Soluble	High	90.90 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Curcumin	3.03	Soluble	High	93.06 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Fisetin	1.55	Soluble	High	111.13 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes

Table 5 (continued)

	SwissADME								
	Consensus log PO/W	Water solubility	GI absorption	TPSA (Å2)	Lipinski's rule	Ghose rule	Veber rule	Egan rule	Muegge rule
Quercetin	1.23	Soluble	High	131.36 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Isorhamnetin	1.65	Soluble	High	120.36 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Genistein	2.04	Soluble	High	90.90 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes
Luteolin	1.73	Soluble	High	111.13 $Å^2$	Yes; 0 violation	Yes	Yes	Yes	Yes

Furthermore, to study the stability of active Apigenin phytocompound, MD simulation for 100 ns was performed.

MD simulation of Apigenin with Delta plus mutant of SARS-CoV-2

MD simulation of Apigenin in complex with Delta plus variant of SARS-CoV-2 for 100 ns was performed to study the stability of protein–ligand complexes. MD simulation data revealed that RMSD of Apigenin, complexed with Delta plus variant of SARS-CoV-2 was stable from the start of the simulation and remained stable upto 100 ns time (Fig. 5A). RMSF of protein–ligand complex was done to study the flexibility and fluctuation in interactive residues in secondary structure of target proteins (Sivaramakrishnan et al. 2020; Kumar et al. 2014).The RMSF plot for Apigenin fit over the Delta plus protein and showed less residual fluctuation in alpha helical and beta strands. Residues ranging from 100 to 300, 730, 900 to 1150 showed the strongest interactions with Apigenin as shown in Fig. 5B. Binding free energy of protein–ligand complexes is composed of Van der Waals energy -145.285 ± 14.315 kJ/mol, Electrostatic energy -7.358 ± 6.263 kJ/mol, Polar solvation energy 60.148 ± 15.417 kJ/mol, SASA energy -14.129 ± 1.345 kJ/mol and Binding energy -106.624 ± 11.965 kJ/mol (Fig. 6).

Hydrogen bond interactions of protein–ligand complexes are shown in Fig. 7A. The Radius of gyration in the range of Apigenin in complex with Delta plus is 4.4–4.9 nm, as shown in Fig. 7B. The Radius of gyration plot establishes the compactness of the Apigenin and Delta plus protein complex and confirms their stability. Solvent accessible range of Apigenin complexed with Delta plus protein is between 650 and 560 nm^2; as shown in Fig. 7C.

Discussion

The mutations in the RBD region of the 18 amino acid long SARS-CoV-2 Spike glycoprotein strengthen the virus's capacity for transmission. To understand the genesis of novel variants, research has focused on the Spike glycoprotein. The Spike protein's RBD region mutations can make closer contact with hACE2, which results in a stronger binding affinity and probably enhanced VOCs infectivity (Chugh et al. 2022). Among all the previously circulating VOCs, the Delta variant, has shown adverse effects on patients and has caused twice as many hospitalizations (Edara et al. 2021). The Delta was found to be 60% more transmissible than the highly infectious Alpha variant identified in the United Kingdom in September 2020 (Duong 2021). The strain undoubtedly contributed to India's massive second wave of cases. According to data available on GISAID, it had spread to 208 countries as of December 19, 2022 (https://gisaid.org/hcov19-variants/). Delta plus, also known as the AY.1 strain which showed a rapid spread, was found to bind easily to the ACE-2 receptor, and was potentially resistant to monoclonal antibody therapy (Roy and Roy 2021). As per GISAID database, apart from these variants, the Omicron variant, which was discovered in Botswana, has now spread to 208 countries as of December 19, 2022 (https://gisaid.org/hcov19-variants/). In regional genomic surveillance, XBB, a recombinant of the BA.2.10.1 and BA.2.75 sublineages, has been reported in 35 countries with a global prevalence of 1.3%. The regional immunological landscape and COVID-19 vaccination rates appear to have an impact on establishing whether the increased immune escape of XBB is sufficient

Table 6 Toxicity prediction of antiviral drugs and phytocompounds using Protox II server

	Protox II						
	LD50 (mg/kg)	Hepato-toxicity	Carcino-genecity	Immuno toxicity	Muta-genicity	Cyto-toxicity	Predicted toxicity class
Name of compound/antibiotic							
Dpnh (NADH)	11,250	Inactive	Inactive	Active	Inactive	Inactive	Class 6
Coenzyme A	11,250	Inactive	Inactive	Inactive	Inactive	Inactive	Class 6
Flavin Adenine Dinucleotide (FAD) Adeflavin	7000	Inactive	Inactive	Active	Inactive	Inactive	Class: 6
Azithromycin	2000	Inactive	Inactive	Active	Inactive	Inactive	Class 4
Colistin	836	Inactive	Inactive	Active	Inactive	Inactive	Class 4
Liquiritin	2300	Inactive	Inactive	Active	Inactive	Inactive	Class 5
Glycyrrhizic acid	1750	Inactive	Inactive	Active	Inactive	Inactive	Class 4
Raltegravir	200	Active	Inactive	Inactive	Inactive	Inactive	Class 3
Lopinavir	5000	Inactive	Inactive	Inactive	Inactive	Inactive	Class 5
Ritonavir	1000	Active	Inactive	Inactive	Inactive	Inactive	Class 4
Doxycycline	1007	Active	Inactive	Active	Inactive	Inactive	Class 4
Ivermectin	27	Inactive	Inactive	Active	Inactive	Inactive	Class 2
Cangrelor	5000	Inactive	Inactive	Active	Inactive	Inactive	Class 5
Nafamostat	1190	Active	Inactive	Active	Inactive	Inactive	Class 4
Abemaciclib	2000	Inactive	Inactive	Inactive	Inactive	Inactive	Class 4
Name of phytocompounds							
Emodin	5000	Inactive	Inactive	Inactive	Active	Inactive	Class 5
Artemisinin	4228	Inactive	Inactive	Active	Inactive	Inactive	Class 5
Aloe-emodin	5000	Inactive	Inactive	Active	Active	Inactive	Class 5
Anthrarufin	5000	Inactive	Inactive	Active	Active	Inactive	Class 5
Alizarine	7000	Inactive	Active	Active	Active	Inactive	Class 5
Dantron	7000	Inactive	Inactive	Active	Active	Inactive	Class 6
1,8 dihydroxy-3-carboxyl-9,10-anthraquinone or rhein	5000	Inactive	Inactive	Inactive	Active	Inactive	Class 5
Cucurbitacin B	14	Inactive	Active	Active	Inactive	Inactive	Class 2
Apigenin	2500	Inactive	Inactive	Inactive	Inactive	Inactive	Class 5
Costunolide	3140	Inactive	Inactive	Active	Inactive	Inactive	Class 5
Nelfinavir	600	Inactive	Inactive	Active	Inactive	Inactive	Class 4
Kaempferol	3919	Inactive	Inactive	Inactive	Inactive	Inactive	Class 5
Curcumin	2000	Inactive	Inactive	Active	Inactive	Inactive	Class 4
Fisetin	159	Inactive	Active	Inactive	Inactive	Inactive	Class 3
Quercetin	159	Inactive	Active	Inactive	Active	Inactive	Class 3
Isorhamnetin	5000	Inactive	Inactive	Active	Inactive	Inactive	Class 5
Genistein	2500	Inactive	Inactive	Inactive	Inactive	Inactive	Class 5
Luteolin	3919	Inactive	Active	Inactive	Active	Inactive	Class 5

to cause new infection waves (Kurhade et al. 2022). Hence, repurposing existing drugs against potential targets of the virus could be an effective strategy to speed up the drug discovery process (Bhardwaj et al. 2021a, b, c).

Molecular docking facilitates the prediction of protein–ligand affinity and the structure of the protein–ligand complex. Additionally, it can be used to investigate the binding difference between the two molecules, which is useful information for lead optimization. In the early stages of the pandemic, Ivermectin was considered as a viable therapeutic drug against SARS-CoV-2. Despite the fact that it violated Lipinski's rule and was immunotoxic, being FDA

Table 7 Drug likeliness prediction of antiviral drugs and phytocompounds

	miLogP	TPSA	Natoms	MW	nON	nOHNH	nviolations
Name of compound/antibiotic							
Dpnh (NADH)	− 3.59	317.64	44	665.45	21	10	3
Coenzyme A	− 4.44	346.58	48	767.54	23	10	3
Flavin Adenine Dinucleotide (FAD) Adeflavin	− 2.69	362.96	53	785.56	24	10	3
Azithromycin	2.73	180.09	52	749	14	5	2
Colistin	− 5.74	490.65	81	1155.45	29	23	3
Liquiritin	0.41	145.91	30	418.4	9	5	0
Glycyrrhizic acid	1.97	267.04	58	822.94	16	8	3
Raltegravir	− 0.81	152.25	32	444.42	11	3	1
Lopinavir	5.69	119.99	46	628.81	9	4	2
Ritonavir	7.51	145.78	50	720.96	11	4	3
Doxycycline	− 0.87	181.61	32	444.44	10	7	1
Ivermectin	4.58	170.09	62	875.11	14	3	2
Cangrelor	1.33	255.92	44	776.37	17	7	3
Nafamostat	2.29	138.08	26	347.38	7	7	1
Abemaciclib	3.94	75	37	506.61	8	1	1
Name of Phytocompound							
Emodin	3.01	94.83	20	270.24	5	3	0
Artemisinin	3.32	54.01	20	282.34	5	0	0
Aloe-emodin	2.42	94.83	20	270.24	5	3	0
Anthrarufin	3.13	74.6	18	240.21	4	2	0
Alizarine	2.9	74.6	18	240.21	4	2	0
Dantron	3.13	74.6	18	240.21	4	2	0
1,8 dihydroxy-3-carboxyl-9,10-anthraquinone or rhein	3	111.9	21	284.22	6	3	0
Cucurbitacin B	2.83	138.2	40	558.71	8	3	1
Apigenin	2.46	90.89	20	270.24	5	3	0
Costunolide	2.89	26.3	17	232.32	2	0	0
Nelfinavir	5.47	101.89	40	567.8	7	4	2
Kaempferol	2.17	111.12	21	286.24	6	4	0
Curcumin	2.3	93.07	27	368.38	6	2	0
Fisetin	1.97	111.12	21	286.24	6	4	0
Quercetin	1.68	131.35	22	302.24	7	5	0
Isorhamnetin	1.99	120.36	23	316.26	7	4	0
Genistein	2.27	90.89	20	270.24	5	3	0
Luteolin	1.97	111.12	21	286.24	6	4	0

approved for other viral infections, repurposing of this medicine became a ray of hope. It showed strongest affinity with the majority of SARS-CoV-2 variants (as justified in our study Table 3) and was found to minimise the probability of mortality in COVID-19 (Bryant et al. 2021; Caly et al. 2020; Krolewiecki et al. 2021; Zaidi and Dehgani-Mobaraki 2022; Mastrangelo et al. 2012). Also, Australia's National COVID-19 Clinical Evidence Taskforce and the World Health Organization suggested the use of Ivermectin only in clinical trials (FAQs 2022). Later on, a review of 10 randomised controlled trials by Roman et al. concluded that Ivermectin is not a viable option for the treatment of COVID-19 patients (Roman et al. 2022). Consequently, it became a weak contender.

Since ancient times compounds extracted from traditional medicinal plants with strong antiviral activity have been used to treat viral infections. It has been found that phytocompounds can inactivate SARS-CoV-2 variants by binding to the Spike glycoprotein and thus inhibit their function like Curcumin, a component of turmeric (Curcuma longa), is believed to have potential properties to prevent or treat diseases such as cancer and viral infections (Manoharan et al.

Table 8 Interactions of apigenin and liquiritin with delta and delta plus variants of SARS-CoV-2

Phytocompound/drug	Delta			Delta plus		
	Binding energy	H-bonding	Hydrophobic interactions	Binding energy	H-bonding	Hydrophobic interactions
Apigenin	− 7	2Arg1012	Thr959, Ala956, Tyr1005, Leu960, Ser1001, Gln963, Thr1004, Gln1008, Gln952, Gln955	− 7.1	-	Thr 959, Gln 1008, Gln 952, Gln 955, Ala 956, Arg 1012, Tyr 1005, Leu 960, Ser 1001, Gln 963, Thr 1004
Liquiritin	− 7.3	5Thr300, Ser50, Asn315, Arg317, Gln626	Cys299, Ala290, Cys289, Glu296, Lys302, Thr628, Thr272, Ser314, Trp631, Gln319	− 7.3	Gln626, Leu627, Ser314, Thr300, Thr272, Ser50	Arg271, Cys299, Ala290, Thr272, Thr628, Pro629, Glu296, Lys302, Cys289

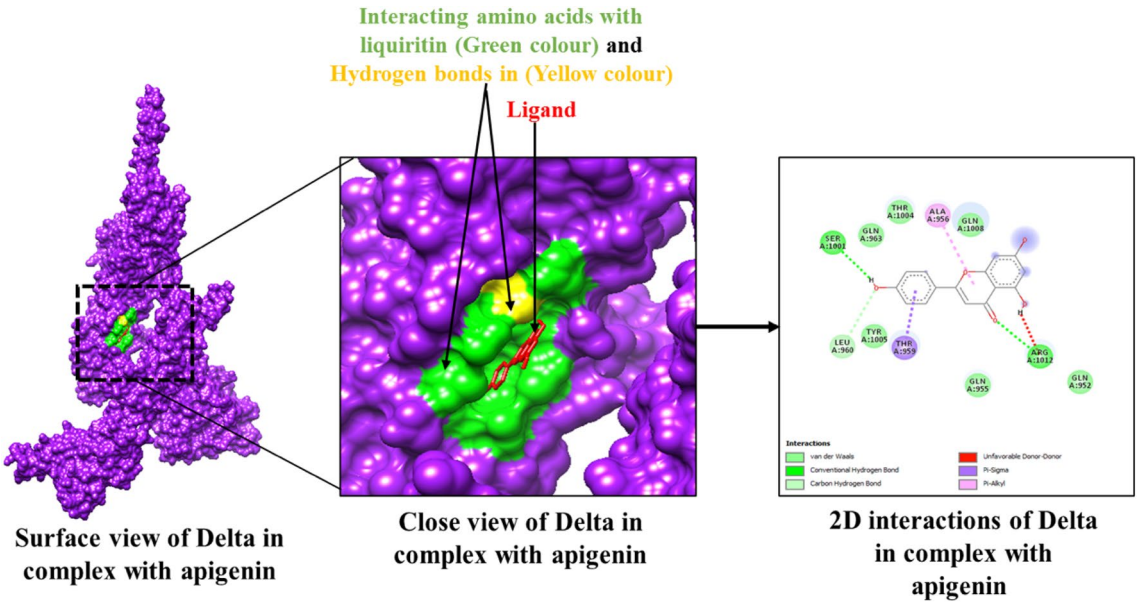

Fig. 1 Interactions of Apigenin with delta variant of SARS-CoV-2 Variant: in close view of delta in complex with Apigenin, purple colour is showing target protein, green colour is showing hydrophobic interactions, yellow colour is showing hydrogen bonding and red colour ligand

2020; Rattis et al. 2021; Singh et al. 2021). Artemisinin and Emodin have also been found to interact with SARS-CoV-2 and inhibit its Spike glycoprotein (Rolta et al. 2021; Nair et al. 2021; Sehailia and Chemat 2021).

All this led to investigation of binding affinity of drugs as well as phytocompounds with the Spike glycoprotein of SARS-CoV-2 using molecular docking. Results from our study show that phytocompounds exhibit the binding affinity as high as drugs. Also, Sathya et al. has reported the promising results of Liquirtin against H1N1 and H3N2 influenza A virus which further confirms its anti-viral drug property and makes it a competitive candidate for the treatment of COVID-19 (Sathya et al. 2020). Zhu et al. also proposed that Liquiritin mimics Type I IFN, which inhibits viral replication (Zhu et al. 2020). Our study also suggested Liquirtin as one of the promising drugs, as it exhibits high and uniform binding affinity with the Spike glycoprotein of all 13 variants (between −7.0 and −8.1 kcal/mol). Although it was found to be immuno-toxic, zero violations of Lipinski's Rule make it a candidate for research.

Similarly various studies have attempted to carry out in silico validation of phytocompounds to cure various diseases (Rolta et al. 2021; Mehta et al. 2021; Salaria et al. 2022). Rolta et al. 2021 (Rolta et al. 2021) also reported that phytocompounds (emodin, aloe-emodin, anthrarufin, alizarine, and dantron) of *R. emodi*as inhibitor of nucleocapsid phosphoprotein of SARS-CoV-2. Some of the bioactive molecules from tea have also shown promising binding affinities

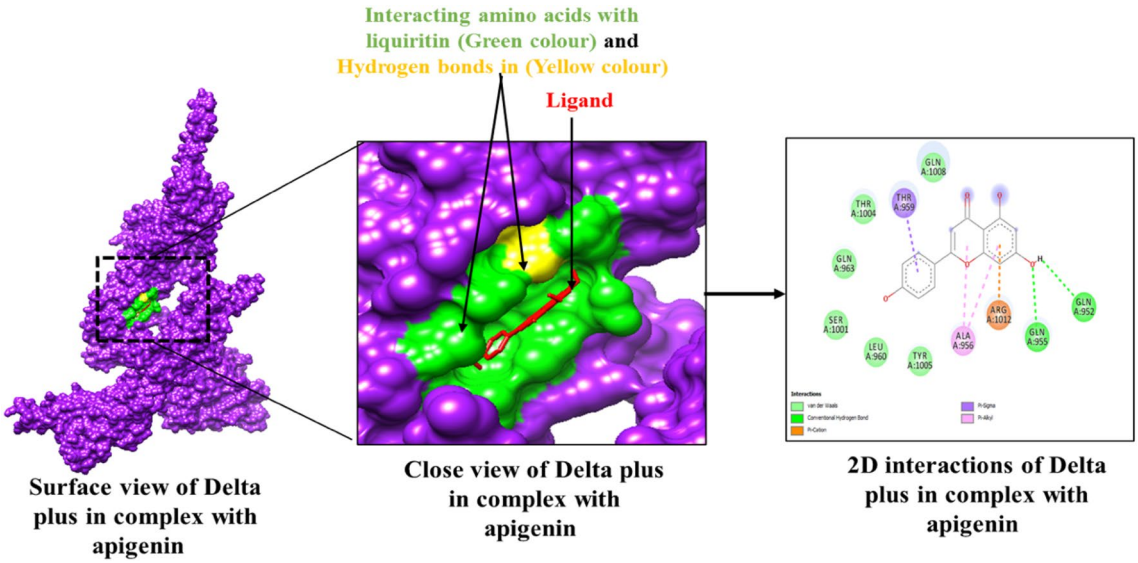

Fig. 2 Interactions of Apigenin with Delta plus variant of SARS-CoV-2 Variant: in close view of Delta plus in complex with Apigenin, purple colour is showing target protein, green colour is showing hydrophobic interactions, yellow colour is showing hydrogen bonding and red colour ligand

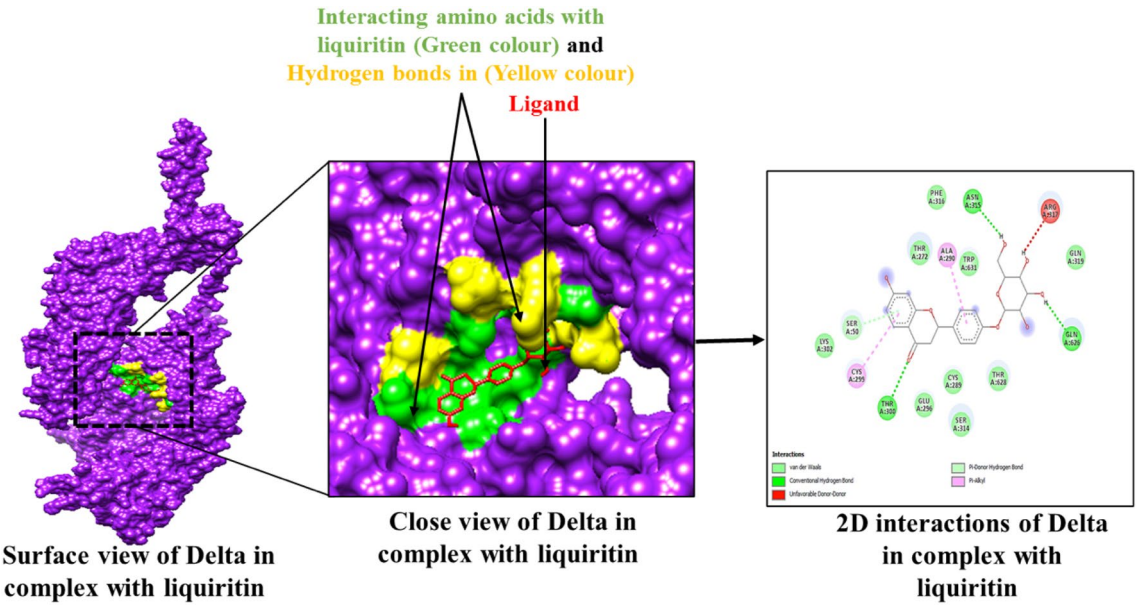

Fig. 3 Interactions of Liquiritin with Delta variant of SARS-CoV-2 Variant: in close view of Delta in complex with Liquiritin, purple colour is showing target protein, green colour is showing hydrophobic interactions, yellow colour is showing hydrogen bonding and red colour ligand

with other proteins of SARS-CoV-2, some of them being NSP15, NSP16 and Mpro (Main protease)(Bhardwaj et al. 2021a, b, c; Singh et al. 2021a, b, c, d; Sharma et al. 2021; Chauhan et al. 2022. Bhardwaj et al. 2021). Hakobyan et al. demonstrated the in vitro effect of Apigenin on African swine fever virus infection by interfering with the viral cell cycle at an early stage in their study, implying that Apigenin could be an effective candidate for extended in vitro and in vivo studies combining dosage effectivity (Hakobyan et al. 2016). In present analysis as well Apigenin expressed the strongest and most consistent binding affinity with all strains (between -6.8 and -7.3 kcal/mol). Additionally, Apigenin exhibited no toxicity and zero violations of Lipinski's rule.

Multiobjective optimisation in drug discovery field implies that a drug should be potent in being active,

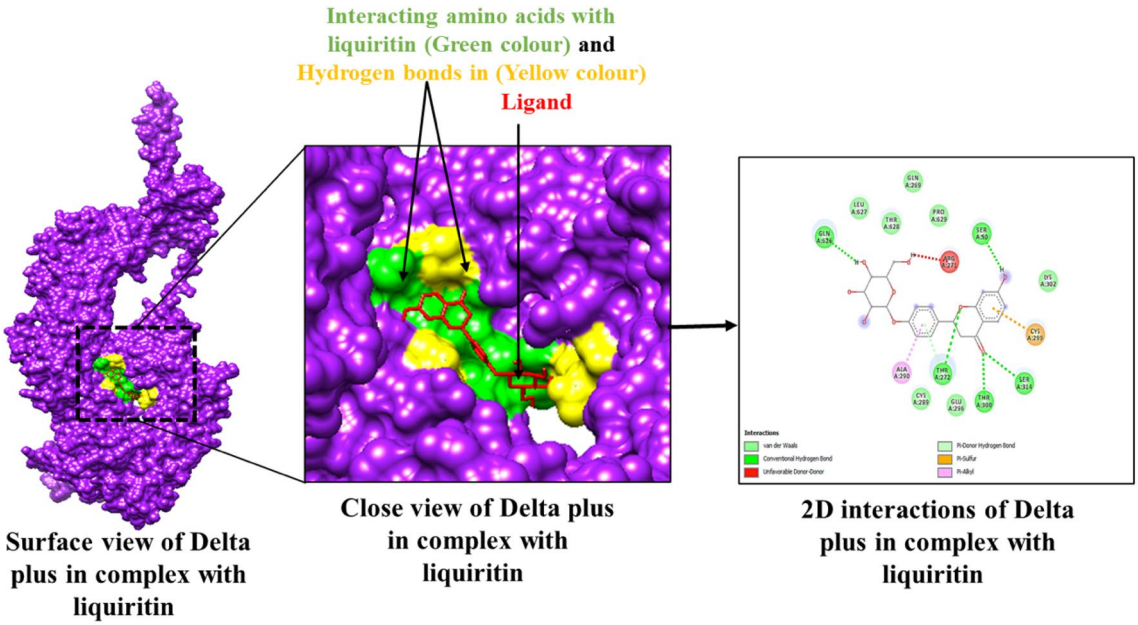

Fig. 4 Interactions of Liquiritin with Delta plus variant of SARS-CoV-2 Variant: in close view of delta plus in complex with Liquiritin, purple colour is showing target protein, green colour is showing hydrophobic interactions, yellow colour is showing hydrogen bonding and red colour ligand

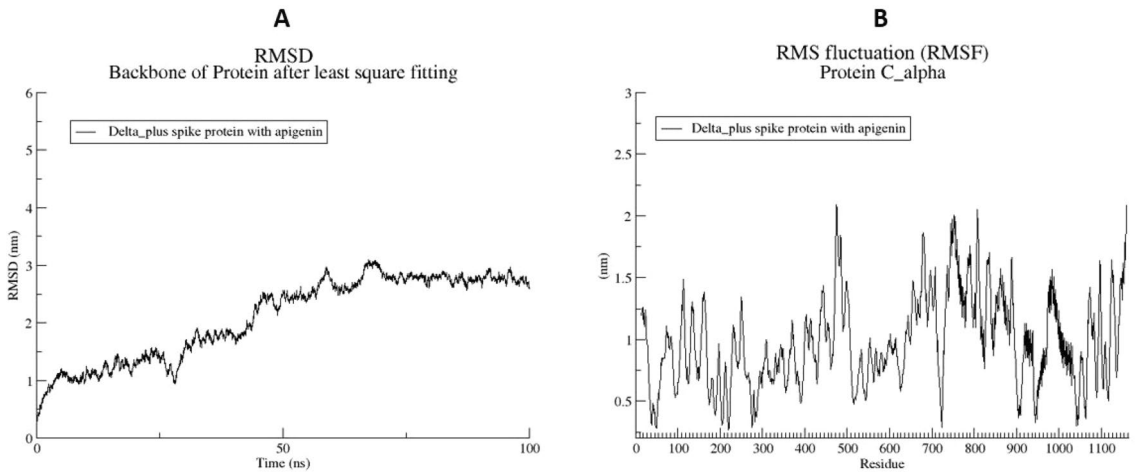

Fig. 5 RMSD and RMSF graph of Apigenin with delta plus variant of SARS-CoV-2 variants for 100 ns: **A** RMSD and **B** RMSF

non-toxic, orally bioavailable, free of side effects, with strong binding affinity, GI absorption (Thomford et al. 2018; Lambrinidis and Tsantili-Kakoulidou 2021). These parameters aid in the screening and recommendation of the prospective drug candidates for in vitro and in vivo studies. Considering all the important parameters, we propose that Apigenin and Liquiritin could be promising options for the treatment of COVID-19 and that they should be investigated further in vitro and in vivo to see if they can be used to build therapeutic strategies to combat future SARS-CoV-2 peaks.

Conclusion

It is imperative that the drugs and phytocompounds not only pass the toxicity prediction and drug likeliness, but they should also have a consistent binding affinity to all the variants. In the present study, 43 drugs and 35 phytocompounds candidates with potential inhibitory effects towards Spike glycoprotein of SARS-CoV-2 were chosen to perform molecular docking studies. Based on our

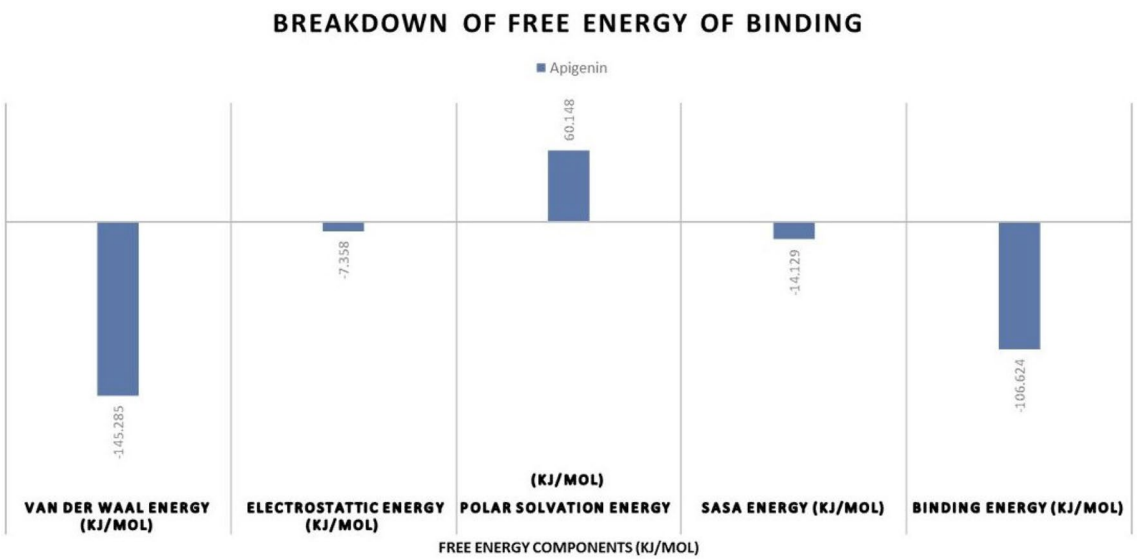

Fig. 6 Breakdown of free energy of binding estimated with gMMPBSA

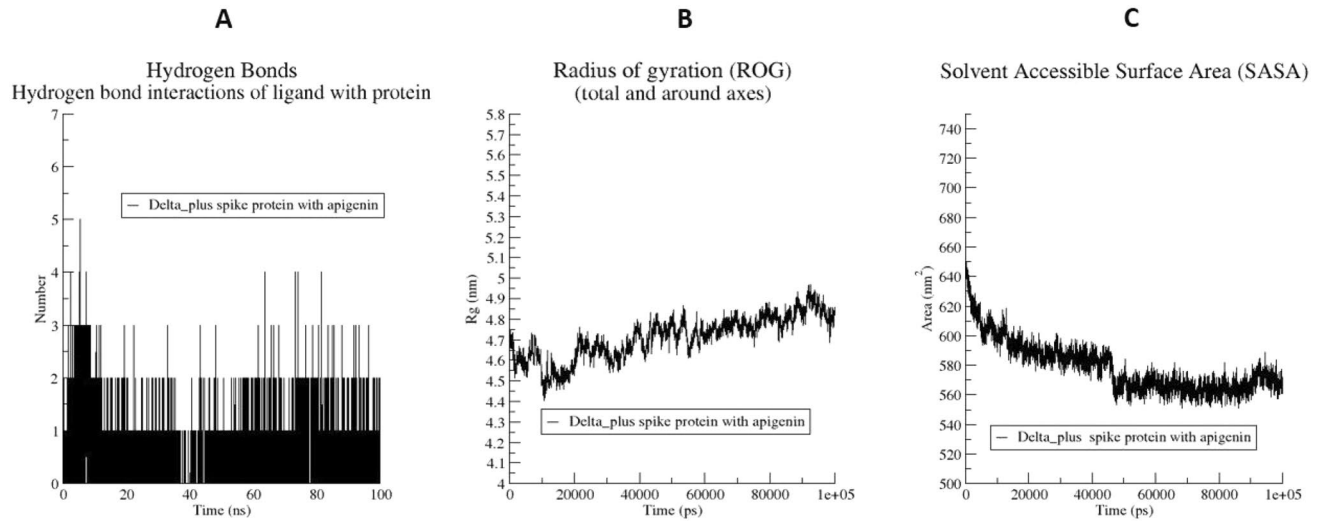

Fig. 7 **A** Hydrogen bond interactions of ligand with protein, **B** Radius of gyration (ROG) and, **C** Solvent accessible surface area

comparative binding affinity analysis, ADMET analysis and druglikeliness profile we have shortlisted Liquiritin (among the repurposing drugs) and Apigenin (among the phytocompounds). MD simulation results confirmed the stability of Apigenin with Delta plus variant. The consistent binding affinities of repurposing drugs and phytocompounds with all the existing variants of SARS-CoV-2 indicates that these maybe effective universally against upcoming variants as well, thus making it one of the largest comparative studies.

Data availablility

All data generated or analysed during this study are included in this published article (and its supplementary information files).

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Declarations

Conflict of interest The authors report there are no competing interests to declare.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

Abraham MJ, Murtola T, Schulz R, Páll S, Smith JC, Hess B et al (2015) GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX 1–2:19–25. https://doi.org/10.1016/j.softx.2015.06.001

Aleem A, Akbar Samad AB, Slenker AK (2022) Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19). StatPearls Publishing, StatPearls, Treasure Island (FL)

Banerjee P, Eckert AO, Schrey AK, Preissner R (2018) ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res 46:W257–W263. https://doi.org/10.1093/nar/gky318

Basu A, Sarkar A, Maulik U (2020) Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2. Sci Rep 10:17699. https://doi.org/10.1038/s41598-020-74715-4

Bhardwaj VK, Singh R, Sharma J, Rajendran V, Purohit R, Kumar S (2021a) Bioactive molecules of tea as potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2. Front Med 8:684020. https://doi.org/10.3389/fmed.2021.684020

Bhardwaj VK, Singh R, Sharma J, Rajendran V, Purohit R, Kumar S (2021b) Identification of bioactive molecules from tea plant as SARS-CoV-2 main protease inhibitors. J Biomol Struct Dyn 39:3449–3458. https://doi.org/10.1080/07391102.2020.1766572

Bhardwaj VK, Singh R, Das P, Purohit R (2021c) Evaluation of acridinedione analogs as potential SARS-CoV-2 main protease inhibitors and their comparison with repurposed anti-viral drugs. Comput Biol Med 128:104117. https://doi.org/10.1016/j.compbiomed.2020.104117

Bryant A, Lawrie TA, Dowswell T, Fordham EJ, Mitchell S, Hill SR et al (2021) Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. Am J Ther 28:e434–e460. https://doi.org/10.1097/MJT.0000000000001402

Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 178:104787. https://doi.org/10.1016/j.antiviral.2020.104787

Chugh A, Khurana N, Verma K, Sehgal I, Rolta R, Vats P et al (2022) Changing dynamics of SARS-CoV-2: a global challenge. Appl Sci 12:5546. https://doi.org/10.3390/app12115546

Darden T, Perera L, Li L, Pedersen L (1999) New tricks for modelers from the crystallography toolkit: the particle mesh Ewald algorithm and its use in nucleic acid simulations. Structure 7:R55-60. https://doi.org/10.1016/S0969-2126(99)80033-1

Dong J, Wang N-N, Yao Z-J, Zhang L, Cheng Y, Ouyang D et al (2018) ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. J Cheminformat 10:29. https://doi.org/10.1186/s13321-018-0283-x

Dotolo S, Marabotti A, Facchiano A, Tagliaferri R (2021) A review on drug repurposing applicable to COVID-19. Brief Bioinform 22:726–741. https://doi.org/10.1093/bib/bbaa288

Duong D (2021) Alpha, Beta, Delta, Gamma: What's important to know about SARS-CoV-2 variants of concern? CMAJ 193:E1059–E1060. https://doi.org/10.1503/cmaj.1095949

Edara V-V, Pinsky BA, Suthar MS, Lai L, Davis-Gardner ME, Floyd K et al (2021) Infection and vaccine-induced neutralizing-antibody responses to the SARS-CoV-2 B.1.617 variants. N Engl J Med 385:664–666. https://doi.org/10.1056/NEJMc2107799

Egan WJ, Merz KM, Baldwin JJ (2000) Prediction of drug absorption using multivariate statistics. J Med Chem 43:3867–3877. https://doi.org/10.1021/jm000292e

FAQs-National COVID-19 Clinical Evidence Taskforce (2022) https://covid19evidence.net.au/faqs/#Ivermectin. Accessed 08 Apr 2022.

Frey JG, Bird CL (2011) Web-based services for drug design and discovery. Expert Opin Drug Discov 6:885–895. https://doi.org/10.1517/17460441.2011.598924

Gobeil SM-C, Janowska K, McDowell S, Mansouri K, Parks R, Stalls V et al (2021) Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity. Science. https://doi.org/10.1126/science.abi6226

Hakobyan A, Arabyan E, Avetisyan A, Abroyan L, Hakobyan L, Zakaryan H (2016) Apigenin inhibits African swine fever virus infection in vitro. Arch Virol 161:3445–3453. https://doi.org/10.1007/s00705-016-3061-y

Hall DC, Ji H-F (2020) A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. Travel Med Infect Dis. https://doi.org/10.1016/j.tmaid.2020.101646

Hess B, Bekker H, Berendsen HJC, Fraaije JGEM (1997) LINCS: a linear constraint solver for molecular simulations. J Comput Chem 18:1463–1472. https://doi.org/10.1002/(SICI)1096-987X(199709)18:12%3c1463::AID-JCC4%3e3.0.CO;2-H

Hu B, Guo H, Zhou P, Shi Z-L (2021) Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19:141–154. https://doi.org/10.1038/s41579-020-00459-7

Khanna K, Raymond W, Jin J, Charbit AR, Gitlin I, Tang M et al (2020) Thiol drugs decrease SARS-CoV-2 lung injury in vivo and disrupt SARS-CoV-2 spike complex binding to ACE2 in vitro. bioRxiv. https://doi.org/10.1101/2020.12.08.415505

Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso DF et al (2021) Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine 37:100959. https://doi.org/10.1016/j.eclinm.2021.100959

Kumar CV, Swetha RG, Anbarasu A, Ramaiah S (2014) Computational analysis reveals the association of threonine 118 methionine mutation in PMP22 resulting in CMT-1A. Adv Bioinform 2014:1–10. https://doi.org/10.1155/2014/502618

Kumari R, Kumar R (2014) Open source drug discovery consortium, Lynn A. *g_mmpbsa*—A GROMACS tool for high-throughput MM-PBSA Calculations. J Chem Inf Model 54:1951–1962. https://doi.org/10.1021/ci500020m

Kurhade C, Zou J, Xia H, Liu M, Chang HC, Ren P et al (2022) Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by parental mRNA vaccine or a BA5-bivalent booster. Nat Med. https://doi.org/10.1038/s41591-022-02162-x

Kushwaha V, Kaur S (2021) Immunostimulatory role of rBmHSP60 from filarial parasite Brugia malayi. Asian Pac J Trop Biomed 11:20. https://doi.org/10.4103/2221-1691.300728

Lambrinidis G, Tsantili-Kakoulidou A (2021) Multi-objective optimization methods in novel drug design. Expert Opin Drug Discov 16(6):647–658. https://doi.org/10.1080/17460441.2021.1867095

Maher MC, Bartha I, Weaver S, di Iulio J, Ferri E, Soriaga L et al (2021) Predicting the mutational drivers of future SARS-CoV-2 variants of concern. Sci Translat Med. https://doi.org/10.1101/2021.06.21.21259286

Manoharan Y, Haridas V, Vasanthakumar KC, Muthu S, Thavoorullah FF, Shetty P (2020) Curcumin: a wonder drug as a preventive measure for COVID19 management. Ind J Clin Biochem 35:373–375. https://doi.org/10.1007/s12291-020-00902-9

Martinez MA (2021) Lack of effectiveness of repurposed drugs for COVID-19 treatment. Front Immunol 12:635371

Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K et al (2012) Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother 67:1884–1894. https://doi.org/10.1093/jac/dks147

Mehta J, Rolta R, Salaria D, Awofisayo O, Fadare OA, Sharma PP et al (2021) Phytocompounds from himalayan medicinal plants as potential drugs to treat multidrug-resistant salmonella typhimurium: an in silico approach. Biomedicines 9:1402. https://doi.org/10.3390/biomedicines9101402

Nair MS, Huang Y, Fidock DA, Polyak SJ, Wagoner J, Towler MJ et al (2021) Artemisia annua L. extracts inhibit the in vitro replication of SARS-CoV-2 and two of its variants. J Ethnopharmacol 274:114016. https://doi.org/10.1016/j.jep.2021.114016

Ni D, Lau K, Turelli P, Raclot C, Beckert B, Nazarov S et al (2021) Structural analysis of the spike of the omicron SARS-COV-2 variant by cryo-EM and implications for immune evasion. Immunology. https://doi.org/10.1101/2021.12.27.474250

Páll S, Abraham MJ, Kutzner C, Hess B, Lindahl E (2015) Tackling exascale software challenges in molecular dynamics simulations with GROMACS. In: Markidis S, Laure E (eds) Solving Software Challenges for Exascale, vol 8759. Springer International Publishing, Cham

Pant R, Joshi A, Maiti P, Nand M, Pande V, Chandra S (2020) Identification of potential mycolyltransferase Ag85C inhibitors of mycobacterium tuberculosis H37Rv via virtual high throughput screening and binding free energy studies. J Mol Graph Model 98:107584. https://doi.org/10.1016/j.jmgm.2020.107584

Parasuraman S (2011) Toxicological screening. J Pharmacol Pharmacother 2:74–79. https://doi.org/10.4103/0976-500X.81895

Pk M, Sundaram KM, RM S (2020) Coronavirus spike (S) glycoprotein (2019-Ncov) targeted siddha medicines Kabasura Kudineer and Thonthasura Kudineer â€“ in silico evidence for corona viral drug. Asian J Pharmaceut Res Health Care 12:20–27. https://doi.org/10.18311/ajprhc/2020/25103

Poratti M, Marzaro G (2019) Third-generation CDK inhibitors: a review on the synthesis and binding modes of Palbociclib, Ribociclib and Abemaciclib. Eur J Med Chem 172:143–153. https://doi.org/10.1016/j.ejmech.2019.03.064

Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS et al (2020) SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med 28:174–184

Rattis BAC, Ramos SG, Celes MRN (2021) Curcumin as a potential treatment for COVID-19. Front Pharmacol 12:675287. https://doi.org/10.3389/fphar.2021.675287

Rolta R, Salaria D, Sharma P, Sharma B, Kumar V, Rathi B et al (2021) Phytocompounds of rheum emodi, thymus serpyllum, and artemisia annua inhibit spike protein of SARS-CoV-2 binding to ACE2 receptor. In Silico Approach Curr Pharmacol Rep 7:135–149. https://doi.org/10.1007/s40495-021-00259-4

Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV (2022) Ivermectin for the treatment of coronavirus disease 2019: a systematic review and meta-analysis of randomized controlled trials. Clin Infect Dis 74:1022–1029. https://doi.org/10.1093/cid/ciab591

Roy B, Roy H (2021) The delta plus variant of COVID-19: will it be the worst nightmare in the SARS-CoV-2 pandemic? J Biomed Sci 8:1–2. https://doi.org/10.3126/jbs.v8i1.38449

Rudrapal M, Khairnar JS, Jadhav GA (2020) Drug repurposing (DR): an emerging approach in drug discovery. In: Badria AF (ed) Drug repurposing-hypothesis molecular aspects and therapeutic applications. IntechOpen

Salaria D, Rolta R, Mehta J, Awofisayo O, Fadare OA, Kaur B et al (2022) Phytoconstituents of traditional Himalayan Herbs as potential inhibitors of Human Papillomavirus (HPV-18) for cervical cancer treatment: an in silico approach. PLoS ONE 17:e0265420. https://doi.org/10.1371/journal.pone.0265420

Sathya B, Karthi S, Ajaijawahar K, Prasath M (2020) Probing the vibrational spectroscopic properties and binding mechanism of anti-influenza agent Liquiritin using experimental and computational studies. Res Chem Intermed 46:4475–4507. https://doi.org/10.1007/s11164-020-04216-6

Scherman D, Fetro C (2020) Drug repositioning for rare diseases: knowledge-based success stories. Therapies 75:161–167. https://doi.org/10.1016/j.therap.2020.02.007

Sehailia M, Chemat S (2021) Antimalarial-agent artemisinin and derivatives portray more potent binding to Lys353 and Lys31-binding hotspots of SARS-CoV-2 spike protein than hydroxychloroquine: potential repurposing of artenimol for COVID-19. J Biomol Struct Dyn 39:6184–6194. https://doi.org/10.1080/07391102.2020.1796809

Sharma J, Kumar Bhardwaj V, Singh R, Rajendran V, Purohit R, Kumar S (2021) An in-silico evaluation of different bioactive molecules of tea for their inhibition potency against non structural protein-15 of SARS-CoV-2. Food Chem 346:128933. https://doi.org/10.1016/j.foodchem.2020.128933

Singh R, Bhardwaj VK, Sharma J, Kumar D, Purohit R (2021a) Identification of potential plant bioactive as SARS-CoV-2 Spike protein and human ACE2 fusion inhibitors. Comput Biol Med 136:104631. https://doi.org/10.1016/j.compbiomed.2021.104631

Singh R, Bhardwaj VK, Das P, Purohit RA (2021b) computational approach for rational discovery of inhibitors for non-structural protein 1 of SARS-CoV-2. Comput Biol Med 135:104555. https://doi.org/10.1016/j.compbiomed.2021.104555

Singh R, Bhardwaj VK, Purohit R (2021c) Potential of turmeric-derived compounds against RNA-dependent RNA polymerase of SARS-CoV-2: an in-silico approach. Comput Biol Med 139:104965. https://doi.org/10.1016/j.compbiomed.2021.104965

Singh R, Bhardwaj VK, Sharma J, Purohit R, Kumar S (2022) In-silico evaluation of bioactive compounds from tea as potential SARS-CoV-2 nonstructural protein 16 inhibitors. J Tradit Complement Med 12:35–43. https://doi.org/10.1016/j.jtcme.2021.05.005

Sivaramakrishnan M, Kandaswamy K, Natesan S, Devarajan RD, Ramakrishnan SG, Kothandan R (2020) Molecular docking and dynamics studies on plasmepsin V of malarial parasite Plasmodium vivax. Informat Med Unlocked 19:100331. https://doi.org/10.1016/j.imu.2020.100331

Chauhan M et al (2022) Theaflavin 3-Gallate Inhibits the Main Protease (Mpro) of SARS-CoV-2 and Reduces Its Count in Vitro. Sci Rep 12(1):13146. https://www.nature.com/articles/s41598-022-17558-5. Accessed 3 Jan 2023

Thomford N, Senthebane D, Rowe A, Munro D, Seele P, Maroyi A et al (2018) Natural products for drug discovery in the 21st century: innovations for novel drug discovery. IJMS 19:1578. https://doi.org/10.3390/ijms19061578

Toor HG, Banerjee DI, Lipsa Rath S, Darji SA (2021) Computational drug re-purposing targeting the spike glycoprotein of SARS-CoV-2 as an effective strategy to neutralize COVID-19. Eur J Pharmacol. https://doi.org/10.1016/j.ejphar.2020.173720

Verma D, Mitra D, Paul M, Chaudhary P, Kamboj A, Thatoi H et al (2021) Potential inhibitors of SARS-CoV-2 (COVID 19) proteases PLpro and Mpro/ 3CLpro: molecular docking and simulation studies of three pertinent medicinal plant natural components. Current Res Pharmacol Drug Discovery 2:100038. https://doi.org/10.1016/j.crphar.2021.100038

Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181:281-292.e6. https://doi.org/10.1016/j.cell.2020.02.058

Wang C, Liu Z, Chen Z, Huang X, Xu M, He T et al (2020) The establishment of reference sequence for SARS-CoV-2 and variation analysis. J Med Virol 92:667–674. https://doi.org/10.1002/jmv.25762

Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P et al (2021) Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19. Cells 10:821. https://doi.org/10.3390/cells10040821

Zaidi AK, Dehgani-Mobaraki P (2022) The mechanisms of action of ivermectin against SARS-CoV-2—an extensive review. J Antibiot 75:60–71. https://doi.org/10.1038/s41429-021-00491-6

Zheng J (2020) SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci 16:1678–1685. https://doi.org/10.7150/ijbs.45053

Zhu J, Deng Y-Q, Wang X, Li X-F, Zhang N-N, Liu Z et al (2020) An artificial intelligence system reveals liquiritin inhibits SARS-CoV-2 by mimicking type I interferon. Sys Biol. https://doi.org/10.1101/2020.05.02.074021