In Silico screening of some antiviral phytochemicals as drug leads against Covid-19

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Abstract

Background: COVID-19 caused by SARS-CoV-2 in December 2019 has become a pandemic hazard to the community health. It is a respiratory difficulty causing fever, dry cough, fatigue, shortness of breath, muscle aches and some instances lead to pneumonia. Coronaviruses have large viral RNA Genomes and are single-stranded positive-sense RNA viruses. The nsp10/nsp16 protein is an important target because it is essential for the virus to replicate, the papain-like protease (Nsp3), the main protease (Nsp5), the primary RNA-dependent RNA polymerase (Nsp12) are also attractive drug targets for this disease. The uses of phytochemicals as therapeutic agents have been increasing in recent years. Some antiviral phytochemicals were taken based on literature survey for this study.

Methods: ADME parameters and drug like nature of phytochemicals were screened using SwissADME web tool. Three dimensional structures of targets are downloaded from Protein Data Bank and docked with phytochemicals & control by using software FlexX.

Results: Morin shows significant results in ADME screening and Drug likeness prediction studies, it shows stable bonding pattern with all four targets in compare to other phytochemicals and control, shows least score in docking and forms maximum number of hydrogen bonds with the active residues of the receptors.

Conclusion: Based on present observation of docking results, ADME parameters and drug like nature, we suggest that **morin** may be a potent new drug candidate against Covid-19.

Keywords: COVID-19, coronavirus, drug target, phytochemicals, Drug likeness, ADME, docking, morin

Introduction

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) & the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are members of the family Coronaviridae and causes mild respiratory diseases. They affect species from animals to humans causing severe

forms of respiratory disease. In the year 2002 SARS-CoV emerged in Guandong province of China. Its transmission caused more than 8000 cases and 774 deaths[1]. No specific antiviral treatment exists to conquer the disease that was earlier ended by control measures such as travel constraint and patient isolation.

In Wuhan, Hubei province of China a new form of pneumonia disease emerged in winter 2019 [2–4]. It was known as SARS-CoV-2 causing the coronavirus disease 2019 (COVID-19) and rapidly spread from animals (pangolins or bats as possible sources) to humans.

COVID-19 has become a pandemic hazard to the community health. It is a respiratory difficulty causing fever, dry cough, fatigue, shortness of breath, muscle aches and some instances lead to pneumonia[5].

The transmission in humans was very fast. As on June 12, 2020, a total of 7553182 confirmed infections were reported worldwide, with 423 349 deaths[6].

The World Health Organization (WHO) strategy to contain the spreading includes the decrease of human-to-human spreading by restraining the contact between individuals, thus preventing diffusion amplification events and communicating critical risk information to all communities[6].

While the diagnosis of COVID-19 is based on the amplification of the viral genome in real-time PCR with specific probes, the current treatment of affected person is limited to a combination of broad-spectrum antiviral drugs[7]. However, in several cases this pharmacological approach has proven to be totally unproductive. Coronaviruses have large viral RNA Genomes and are single-stranded positive-sense RNA viruses[8].

The nsp10/16 is a complex of two critical proteins mapped by scientists from Northwestern University, Feinberg School of Medicine, USA. This protein is also known as RNA methyltransferase or MTase. Complex nature makes it more difficult to work with. The alliance of the two pieces jointly is essential to make a functional protein. These proteins transform the genetic material of the virus to construct it and seem like the host (human) cell RNA. This permits the virus to hide from the cells, providing it time to reproduce. This is a vital target because it is essential for the virus to replicate. If a drug can be developed to inhibit nsp10/nsp16, the immune system should be able to identify the virus and eliminate it earlier[9]. Beside this, several other proteins having roles in viral replication, gene expression etc. like the papain-like protease (Nsp3), the main protease (Nsp5), the primary RNA-dependent RNA polymerase (Nsp12), an exoribonuclease (Nsp14), an endonuclease (Nsp15) etc. are also attractive drug targets for this disease[10].

Plants have naturally developed over the years in varied climate conditions on earth and have been bestowed with affluent composite of secondary metabolites/phytochemicals with broad

pharmacokinetic spectrum. Around 2500 medicinal plant species have been documented worldwide[11, 12] to treat a myriad of inflictions and ailments. Polyphenols, alkaloids, flavonoids, saponins, quinones, terpenes, proanthocyanidins, lignins, tannins, polysaccharides, steroids, thiosulfonates, coumarins etc. are prominent bioactive phytochemicals, which have been studied to combat viral diseases[14-20] (Table 1). Therefore, the present study was conducted to discover potent anti-COVID-19 natural compounds. In this study hydroxychloroquine is taken as positive control since it is reported to be efficient in Chinese COV-19 patients[13].

Table 1: Some antiviral phytochemicals

Sl. No.	Phytochemicals	Plant (part)
1	Baicalin	*Scutellaria baicalensis* (roots)
2	Chalcones	*Glycyrrhiza inflate* (roots)
3	Dammarenolic acid	*Aglaia* sp. (bark)
4	Decanoylphorbol-13 acetate	*Croton mauritianus* (leaves)
5	Excoecarianin, Loliolide	*Phyllanthus urinaria* (whole plant)
6	Honokiol	Magnolia tree (roots, bark)
7	Jubanines	*Ziziphus jujuba* (roots)
8	Limonoids	*Swietenia macrophylla* (stem)
9	Oleanane	*Camellia japonica* (flowers)
10	Quercetin	*Embelia ribes* (seeds)
11	Saikosaponins	*Bupleurum kaoi* (roots)
12	Sennoside A	*Rheum palmatum* (roots)
13	Silvestrol	*Aglaia foveolata* (leaves, bark)
14	SJP-L-5	*Schisandra micrantha* (roots)
15	Spiroketalenol	*Tanacetum vulgare* (rhizome)
16	Swerilactones	*Swertia mileensis* (whole plant)
17	Xanthohumol	*Humulus lupulus* (whole plant)
18	Oxyresveratrol	*Artocarpus lakoocha*
19	Saikosaponin B2	*Bupleurum kaoi* (Root)
20	Tangeretin and nobiletin	*Citrus reticulate* (Pericarps)
21	Jatrophane ester	*Euphorbia amygdaloides* spp. and *semiperfoliata* (Whole plant)
22	Glycyrrhizic acid	*Glycyrrhiza radix* (Roots)
23	Quercetin 3-rhamnoside	*Houttuynia cordata* (Aerial parts)

24	Samarangenin B	*Limonium sinense* (Root)
25	LPRP-Et-97543	*Liriope platyphylla* (Root)
26	Tetranortriterpenoid 1-cinnamoyl-3, 11-dihydroxymeliacarpin (CDM)	*Melia azedarach* L. (Leaves)
27	Lignin–carbohydrate complex	*Prunella vulgaris* (*F*ruit spikes)
28	Pterocarnin A	*Pterocarya stenoptera* (Bark)
29	Chalepin and pseudane IX	*Ruta angustifolia* (Leaves)
30	Manassantin B	*Saururus chinensis* (Root)
31	Dicaffeoylquinic acids	*Schefflera heptaphylla* (Leaf stalks)
32	Scopadulcic acid B	*Scoparia dulcis* L. (Whole plant)
33	5,7,4' trihydroxy-8-methoxyflavone (F36)	*Scutellaria baicalensis* (Root)
34	Naringin	grape and orange (skin)
35	Myricetin	*Myrica cerifera*
36	Inophyllum_B	*Calophyllum inophyllum*
37	Inophyllum_P	*Calophyllum inophyllum*
38	Pericalline	*Catharanthus roseus* / *C. lanceus*
39	Chrysophanic acid	*Dianella longifolia*
40	Nordihydroguaiaretic acid	*Larrea divaricata*
41	Retrojusticidin B	*Phyllanthus myrtifolius*
42	Emodin	*Rheum sp.* and *Polygonum sp.*
43	Gingerol	Zingiberis rhizome
44	Anthraquinone	*Dianella longifolia*
45	Methyl rosmarinate	*Hyptis atrorubens Poit*
46	Licoleafol	*Glycyrrhiza uralensis*
47	Amaranthin	*Amaranthus tricolor*
48	Calceolarioside B	*Fraxinus sieboldiana*
49	Papaverine	*Papaver somniferum*
50	Biopterin	*Crithidia fasciculata*
51	Buchapine	*Euodia roxburghiana*
52	Caribine	*Hymenocallis arencola*

53	Lycorine	*Clivia miniata*
54	Fisetin	*Rhus spp.*
55	Morin	*Prunus dulcis*, *Chlorophora tinctoria*, *Psidium guajava* etc.
56	Luteolin	*Matricaria inodora* L.
57	Rutin	*Fagopyrum esculentum*
58	Taxifolin	*Acacia catechu*
59	Oleanolic acid	*Prosopis glandulosa*
60	Betulinic acid	*Syzigium claviflorum*

Materials and Methods

The Ligands

Antiviral phytochemicals were taken based on literature survey, the structure of these phytochemicals and positive control hydroxychloroquine were retrieved from PubChem Compound and by drawing using ChemOffice tools. The three dimensional structure of these compounds in sdf format were generated using OpenBabel software [21].

Drug likeness study and ADME Screening

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process. SwissADME web tool was used to predict ADME parameters and drug like nature of phytochemicals[22].

The receptor

The structures of drug targets: the nsp10/nsp16 protein (RNA methyltransferase or MTase), the papain-like protease (Nsp3), the main protease (Nsp5), the primary RNA-dependent RNA polymerase (Nsp12) are downloaded from RCSB Protein Data Bank (http://www.rcsb.org).

Active site identification

The active sites of targets were identified by the FlexX software[23].

Protein – Ligand interaction using FlexX

Docking is a term used for computational schemes that attempt to find the best matching between two molecules: a receptor and ligand[24]. The receptors were docked with the control and phytochemicals using software FlexX. The active site amino acids were defined in the target molecule during the target preparation. The SDF file of all the compounds was loaded in FlexX

as docking library. The output file gave the energy values in Kcal/mol. For each docked molecule, this value was noted down.

Results

The phytochemicals selected for the study with their SMILES were noted in table 2.

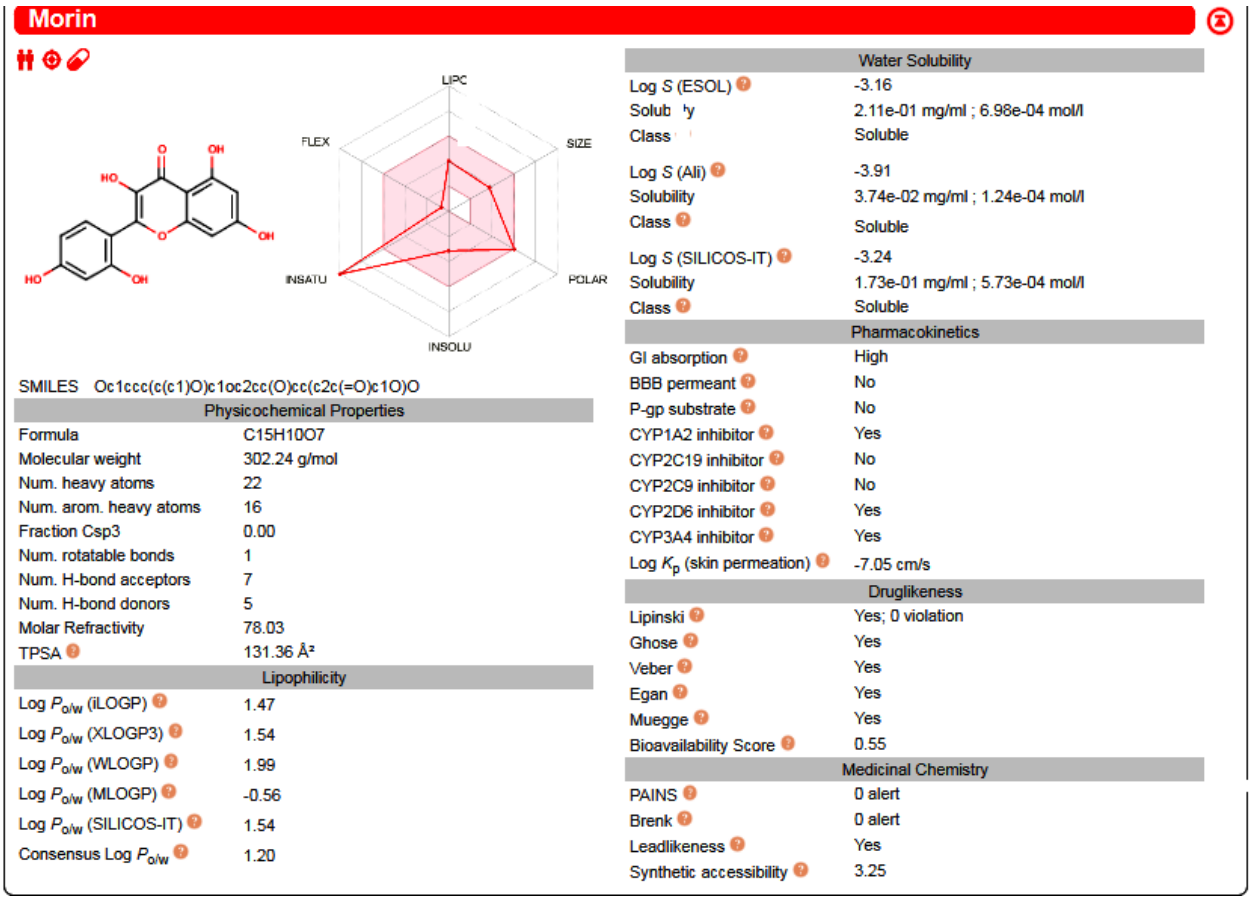
Table 2: Compounds with their SMILES

Compounds	SMILES
Baicalin	C1=CC=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC4C(C(C(C(O4)C(=O)O)O)O)O)O)O
Dammarenolic acid	CC(=CCCC(C)(C1CCC2(C1CCC3C2(CCC(C3(C)CCC(=O)O)C(=C)C)C)C)O)C
Excoecarianin	C1C2C3C(C(C(O2)OC(=O)C4=CC(=C(C(=C4)O)O)O)OC(=O)C5=CC(=C(C6=C5C7C(=CC(=O)C(C7(O)O)(O6)O)C(=O)O3)O)O)OC(=O)C8=C(C(=C(C(=C8)C9=C(C(=C(C=C9C(=O)O1)OC1=C(C(=C(C=C1C(=O)OC1C2C(C(COC(=O)C3=CC(=C(C(=C3C3=C(C(=C(C=C3C(=O)O2)O)O)O)O)O)O)OC1OC(=O)C1=CC(=C(C(=C1)O)O)O)OC(=O)C1=CC(=C(C(=C1)O)O)O)O)O)O)O)O)O)O)O
Loliolide	CC1(CC(CC2(C1=CC(=O)O2)C)O)C
Honokiol	C=CCC1=CC(=C(C=C1)O)C2=CC(=C(C=C2)O)CC=C
Oleanane	CC1(CCC2(CCC3(C(C2C1)CCC4C3(CCC5C4(CCCC5(C)C)C)C)C)C)C
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Sennoside A	C1=CC2=C(C(=C1)OC3C(C(C(C(O3)CO)O)O)O)C(=O)C4=C(C2C5C6=C(C(=CC=C6)OC7C(C(C(C(O7)CO)O)O)O)C(=O)C8=C5C=C(C=C8O)C(=O)O)C=C(C=C4O)C(=O)O
Silvestrol	COC1C(OC(CO1)C(CO)O)OC2=CC3=C(C(=C2)OC)C4(C(C(C(C4(O3)C5=CC=C(C=C5)OC)C6=CC=CC=C6)C(=O)OC)O)O
SJP-L-5	CN(C)C1=CC=C(C=C1)C2=C(C3=C(C=C2C(=O)OC)OCO3)OC
Xanthohumol	CC(=CCC1=C(C(=C(C=C1O)OC)C(=O)C=CC2=CC=C(C=C2)O)O)C
Spiroketalenol	CC#CC#C\C=C1/C=CC2(O1)CCCCO2
Licochalcone	CC(C)(C=C)C1=C(C=C(C(=C1)C=CC(=O)C2=CC=C(C=C2)O)OC)O
Chalcone	C1=CC=C(C=C1)C=CC(=O)C2=CC=CC=C2
Decanoylphorbol-13 acetate	CCCCCCCCCC(=O)OC1C(C2(C(C=C(CC3(C2C=C(C3=O)C)O)CO)C4C1(C4(C)C)OC(=O)C)O)C
Jubanine A	CCC(C)C1C(=O)NC=CC2=C(C=CC(=C2)OC3CCN(C3C(=O)N1)C(=O)C(CC4=CC=CC=C4)NC(=O)C(CC5=CC=CC=C5)N(C)C)OC
Jubanine B	CN(C)C(CC1=CC=CC=C1)C(=O)NC(CC2=CC=CC=C2)C(=O)N3CCC4C3C(=O)NC(C(=O)NC=CC5=C(C=CC(=C5)O4)OC)CC6=CC=CC=C6
3-Hydroxy Caruilignan C	COC1=CC(=CC(=C1OC)O)C2C3COC(=O)C3CO2
Limonin	CC1(C2CC(=O)C3(C(C24COC(=O)CC4O1)CCC5(C36C(O6)C(=O)OC5C7=COC=C7)C)C)C

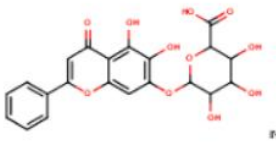
Oxyresveratrol	C1=CC(=C(C=C1O)O)C=CC2=CC(=CC(=C2)O)O
Saikosaponin B2	CC1C(C(C(C(O1)OC2CCC3(C(C2(C)CO)CCC4(C3C=CC5=C6CC(CCC6(C(CC54C)O)CO)(C)C)C)C)O)OC7C(C(C(C(O7)CO)O)O)O)O
Tangeretin	COC1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C(=C3OC)OC)OC)OC
Nobiletin	COC1=C(C=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C(=C3OC)OC)OC)OC)OC
Jatrophane ester	CC1C=CC(C(C(C(C(=C)C(C2C(C1=O)CC(C2C(=O)COC(=O)C3=CC=CC=C3)(C)OC(=O)C)OC(=O)C(C)C)OC(=O)C4=CC=CC=C4)OC(=O)C)OC(=O)C)(C)C
Glycyrrhizic acid	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(C(O4)C(=O)O)O)O)OC5C(C(C(C(O5)C(=O)O)O)O)O)C)C(=O)C=C6C3(CCC7(C6CC(CC7)(C)C(=O)O)C)C)C)C
Quercetin 3-rhamnoside	CC1C(C(C(C(O1)OC2=C(OC3=CC(=CC(=C3C2=O)O)O)C4=CC(=C(C=C4)O)O)O)O)O
LPRP-Et-97543	CC1=C(C2=C(C=C1O)OCC(C2=O)CC3=CC=C(C=C3)O)O
Chalepin	CC(C)(C=C)C1=CC2=CC3=C(C=C2OC1=O)OC(C3)C(C)(C)O
Manassantin B	CC1C(C(OC1C2=CC(=C(C=C2)OC(C)C(C3=CC4=C(C=C3)OCO4)O)OC)C5=CC(=C(C=C5)OC(C)C(C6=CC(=C(C=C6)OC)OC)O)OC)C
Dicaffeoylquinic acid	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)OC(=O)C=CC3=CC(=C(C=C3)O)O)O
Scopadulcic acid B	CC12CCC3(C1)C(CC(C4C3(CCCC4(C)C(=O)O)C)OC(=O)C5=CC=CC=C5)CC2=O
Naringin	CC1C(C(C(C(O1)OC2C(C(C(OC2OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC=C(C=C5)O)O)CO)O)O)O)O)O
Myricetin	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
Inophyllum_B	CC1C(OC2=C(C1O)C3=C(C(=CC(=O)O3)C4=CC=CC=C4)C5=C2C=CC(O5)(C)C)C
Inophyllum_P	CC1C(OC2=C(C1O)C3=C(C(=CC(=O)O3)C4=CC=CC=C4)C5=C2C=CC(O5)(C)C)C
Pericalline	CC=C1CN2CCC1C(=C)C3=C(C2)C=C4C=CNC4=C3
Chrysophanic acid	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=CC=C3O
Nordihydroguaiaretic acid	CC(CC1=CC(=C(C=C1)O)O)C(C)CC2=CC(=C(C=C2)O)O
Retrojusticidin B	COC1=CC2=CC3=C(COC3=O)C(=C2C=C1OC)C4=CC5=C(C=C4)OCO5
Emodin	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)O
Gingerol	CCCCCC(CC(=O)CCC1=CC(=C(C=C1)O)OC)O
Anthraquinone	C1=CC=C2C(=C1)C(=O)C3=CC=CC=C3C2=O
Methyl rosmarinate	COC(=O)C(CC1=CC(=C(C=C1)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O
Licoleafol	CC(=CCC1=C2C(=C(C=C1O)O)C(=O)CC(O2)C3=CC(=C(C=C3)O)O)CO
Amaranthin	C1C(NC(=CC1=CC=[N+]2C(CC3=CC(=C(C=C32)O)OC4C(C(C(C(O4)CO)O)O)OC5C(C(C(C(O5)C(=O)O)O)O)O)C(=O)[O-])C(=O)O)C(=O)O
Calceolarioside B	C1=CC(=C(C=C1CCOC2C(C(C(C(O2)COC(=O)C=CC3=CC(=C(C=C3)O)O)O)O)O)O)O

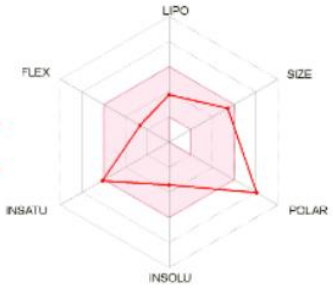
Papaverine	COC1=C(C=C(C=C1)CC2=NC=CC3=CC(=C(C=C32)OC)OC)OC
Biopterin	CC(C(C1=CN=C2C(=N1)C(=O)NC(=N2)N)O)O
Buchapine	CC(=CCC1(C(=O)C2=CC=CC=C2NC1=O)C(C)(C)C=C)C
Caribine	C1CC2C=C3C(CN4C3C(C2NC1)C5=CC6=C(C=C5C4)OCO6)O
Lycorine	C1CN2CC3=CC4=C(C=C3C5C2C1=CC(C5O)O)OCO4
Fisetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O)O
Morin	C1=CC(=C(C=C1O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
Luteolin	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O
Rutin	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O
Taxifolin	C1=CC(=C(C=C1C2C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Oleanolic acid	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C(=O)O)C
Betulinic acid	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C(=O)O
Hydroxychloroquine	CCN(CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl)CCO

For any molecule to become a drug it should not have any toxic or allergenic effects and it should possess all the ADME properties. ADME screening and Drug likeness properties of some phytochemicals were shown below



Baicalin



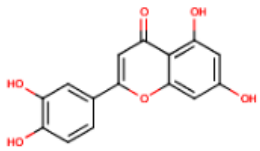


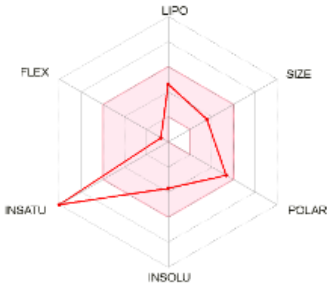
SMILES OC(=O)C1OC(Oc2cc3oc(cc(=O)c3c(c2O)O)c2ccccc2)C(C(C1O)O)O

Physicochemical Properties	
Formula	C21H18O11
Molecular weight	446.36 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	16
Fraction Csp3	0.24
Num. rotatable bonds	4
Num. H-bond acceptors	11
Num. H-bond donors	6
Molar Refractivity	106.72
TPSA	187.12 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.59
Log $P_{o/w}$ (XLOGP3)	1.11
Log $P_{o/w}$ (WLOGP)	0.14
Log $P_{o/w}$ (MLOGP)	-1.63
Log $P_{o/w}$ (SILICOS-IT)	-0.10
Consensus Log $P_{o/w}$	0.22

Water Solubility	
Log *S* (ESOL)	-3.41
Solubility	1.73e-01 mg/ml ; 3.87e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.63
Solubility	1.04e-02 mg/ml ; 2.33e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-2.22
Solubility	2.67e+00 mg/ml ; 5.98e-03 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.23 cm/s
Druglikeness	
Lipinski	No; 2 violations: NorO>10, NHorOH>5
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 3 violations: TPSA>150, H-acc>10, H-don>5
Bioavailability Score	0.11
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	5.09

Luteolin



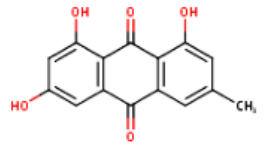


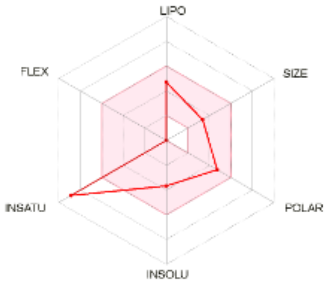
SMILES Oc1cc(O)c2c(c1)oc(cc2=O)c1ccc(c(c1)O)O

Physicochemical Properties	
Formula	C15H10O6
Molecular weight	286.24 g/mol
Num. heavy atoms	21
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	6
Num. H-bond donors	4
Molar Refractivity	76.01
TPSA	111.13 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.86
Log $P_{o/w}$ (XLOGP3)	2.53
Log $P_{o/w}$ (WLOGP)	2.28
Log $P_{o/w}$ (MLOGP)	-0.03
Log $P_{o/w}$ (SILICOS-IT)	2.03
Consensus Log $P_{o/w}$	1.73

Water Solubility	
Log *S* (ESOL)	-3.71
Solubility	5.63e-02 mg/ml ; 1.97e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.51
Solubility	8.84e-03 mg/ml ; 3.09e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-3.82
Solubility	4.29e-02 mg/ml ; 1.50e-04 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.25 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: catechol_A
Brenk	1 alert: catechol
Leadlikeness	Yes
Synthetic accessibility	3.02

Emodin



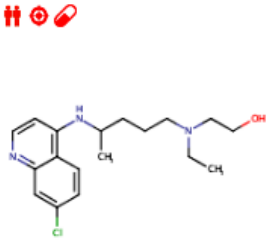


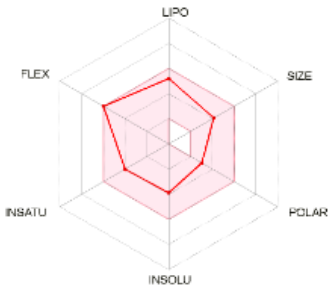
SMILES Cc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)cc(c1)O

Physicochemical Properties	
Formula	C15H10O5
Molecular weight	270.24 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	12
Fraction Csp3	0.07
Num. rotatable bonds	0
Num. H-bond acceptors	5
Num. H-bond donors	3
Molar Refractivity	70.78
TPSA	94.83 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.81
Log $P_{o/w}$ (XLOGP3)	2.72
Log $P_{o/w}$ (WLOGP)	1.89
Log $P_{o/w}$ (MLOGP)	0.36
Log $P_{o/w}$ (SILICOS-IT)	2.55
Consensus Log $P_{o/w}$	1.87

Water Solubility	
Log *S* (ESOL)	-3.67
Solubility	5.74e-02 mg/ml ; 2.12e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.37
Solubility	1.17e-02 mg/ml ; 4.31e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-3.91
Solubility	3.36e-02 mg/ml ; 1.24e-04 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.02 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	2.57

Hydroxychloroquine





SMILES OCCN(CCCC(Nc1ccnc2c1ccc(c2)Cl)C)CC

Physicochemical Properties	
Formula	C18H26ClN3O
Molecular weight	335.87 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	10
Fraction Csp3	0.50
Num. rotatable bonds	9
Num. H-bond acceptors	3
Num. H-bond donors	2
Molar Refractivity	98.57
TPSA	48.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.58
Log $P_{o/w}$ (XLOGP3)	3.58
Log $P_{o/w}$ (WLOGP)	3.59
Log $P_{o/w}$ (MLOGP)	2.35
Log $P_{o/w}$ (SILICOS-IT)	3.73
Consensus Log $P_{o/w}$	3.37

Water Solubility	
Log *S* (ESOL)	-3.91
Solubility	4.17e-02 mg/ml ; 1.24e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.28
Solubility	1.75e-02 mg/ml ; 5.22e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-6.35
Solubility	1.50e-04 mg/ml ; 4.46e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.81 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: Rotors>7, XLOGP3>3.5
Synthetic accessibility	2.82

ADME and drug likeness screening results of some phytochemicals and control

Three dimensional structures of targets are downloaded from Protein Data Bank having PDB ids: 6W75, 6W9C, 6LU7 and 6M71 for the nsp10/nsp16 protein (RNA methyltransferase or MTase), the papain-like protease (Nsp3), the main protease (Nsp5) and RNA-dependent RNA polymerase (Nsp12) respectively.

Interaction energies between ligand and receptor play the most crucial role in drug designing. In this work, drug targets the nsp10/nsp16 protein (RNA methyltransferase or MTase), the papain-like protease (Nsp3), the main protease (Nsp5) and RNA-dependent RNA polymerase (Nsp12) and the interactions of the compounds were studied using FlexX. The docking results of compounds with targets are described in table 3. The docking poses are shown in Figures (Figure 1 – Figure 5).

Table 3: Docking results of targets with phytochemicals and control

Phytochemicals	**Docking Score (Kcal/mol)**			
	NSP10 - NSP16 Complex	**Papain-like protease**	**RNA-dependent RNA polymerase**	**COVID-19 main protease**
Baicalin	-19.7773	**-34.3309**	-19.3806	-12.1868
Dammarenolic acid	-7.2746	-8.3572	-2.6079	2.5649
Excoecarianin	0.0000	0.0000	0.0000	0.0000
Loliolide	-12.3698	-14.5091	-11.4858	-8.0941
Honokiol	-15.9008	-13.9542	-15.7179	-8.6464
Oleanane	0.0000	0.0000	0.0000	0.0000
Quercetin	-24.5804	-24.9869	-20.6509	-12.0769
Sennoside A	-11.2257	-21.5574	-13.4283	2.0780
Silvestrol	-6.4271	-14.5208	-7.9343	4.6139
SJP-L-5	-16.4261	-16.8003	-12.8650	-5.8154
Xanthohumol	-16.9845	-24.9632	-16.9412	-8.4929
Spiroketalenol	-14.9469	-12.8823	-14.8976	-5.3747
Licochalcone	-14.6707	-19.1733	-13.2370	-7.4708
Chalcone	-14.8018	-17.7265	-14.4728	-8.5971
Decanoylphorbol-13 acetate	-2.5114	-4.3715	-1.0579	6.5114
Jubanine A	-16.7469	-28.0104	-9.8798	-2.0363

Jubanine B	0.0000	0.0000	0.0000	0.0000
3-Hydroxy Caruilignan C	-14.8918	-17.8282	-14.5065	-5.4153
Limonin	0.0000	0.0000	0.0000	0.0000
Oxyresveratrol	-23.2724	-21.5388	-18.6387	-15.3810
Saikosaponin B2	0.0000	0.0000	0.0000	0.0000
Tangeretin	-13.5612	-12.9554	-9.9507	-1.3688
Nobiletin	-17.2219	-13.2152	-9.4153	-2.7587
Jatrophane ester	0.0000	0.0000	0.0000	0.0000
Glycyrrhizic acid	0.0000	0.0000	0.0000	0.0000
Quercetin 3-rhamnoside	-24.6582	-27.3896	-21.2587	-13.0196
LPRP-Et-97543	-20.5395	-23.0514	-19.8869	-14.6944
Chalepin	-15.0850	-15.5800	-11.4380	-4.4533
Manassantin B	-12.4506	-24.5615	-8.2997	10.8517
Dicaffeoylquinic acid	-21.7308	-24.2442	-17.0935	-3.3438
Scopadulcic acid B	0.0000	0.0000	0.0000	0.0000
Naringin	-14.5846	-25.7657	-13.6635	-3.7149
Myricetin	-24.5445	-24.8053	-20.7303	-11.4399
Inophyllum_B	-14.3457	-18.4011	-16.6309	-6.3468
Inophyllum_P	-14.3457	-18.4011	-16.6309	-6.3468
Pericalline	-16.3447	-20.8096	-11.5925	-11.7141
Chrysophanic acid	-20.8292	-22.4865	-20.0624	-14.3095
Nordihydroguaiaretic acid	-18.3887	-21.6118	-14.2268	-11.5398
Retrojusticidin B	-12.8700	-23.3895	-16.3522	-7.3189
Emodin	-21.4040	-23.1325	-21.6234	**-20.0202**
Gingerol	-13.9236	-13.5592	-9.9803	-1.4682
Anthraquinone	-12.1782	-15.7292	-13.9016	-8.0614
Methyl rosmarinate	-23.5380	-26.3787	-16.0964	-5.6176
Licoleafol	-16.5607	-26.5293	-15.9209	-11.1106
Amaranthin	-16.7487	-29.2696	-18.8189	-10.5730
Calceolarioside B	-21.5665	-33.3063	-14.0840	-8.3660
Papaverine	-10.5395	-13.0222	-11.9049	-4.6477
Biopterin	-22.4536	-26.9995	-22.0282	-15.6592

Buchapine	-11.2879	-15.4712	-10.8268	-5.6774
Caribine	-21.4095	-20.7228	-16.7849	-15.5639
Lycorine	-19.0653	-28.8497	-17.4176	-10.3894
Fisetin	-23.8578	-24.2011	-21.7482	-13.5647
Morin	**-26.8255**	-24.9316	-23.6366	-12.7982
Luteolin	-24.5968	-25.9438	**-24.3635**	-10.9155
Rutin	-15.5553	-27.0507	-17.3833	-9.4748
Taxifolin	-24.8729	-25.5836	-21.3850	-15.6423
Oleanolic acid	0.0000	0.0000	0.0000	0.0000
Betulinic acid	-8.7601	-10.5598	-6.1947	-1.7703
Hydroxychloroquine	**-16.8433**	**-17.4223**	**-15.7864**	**-6.7979**

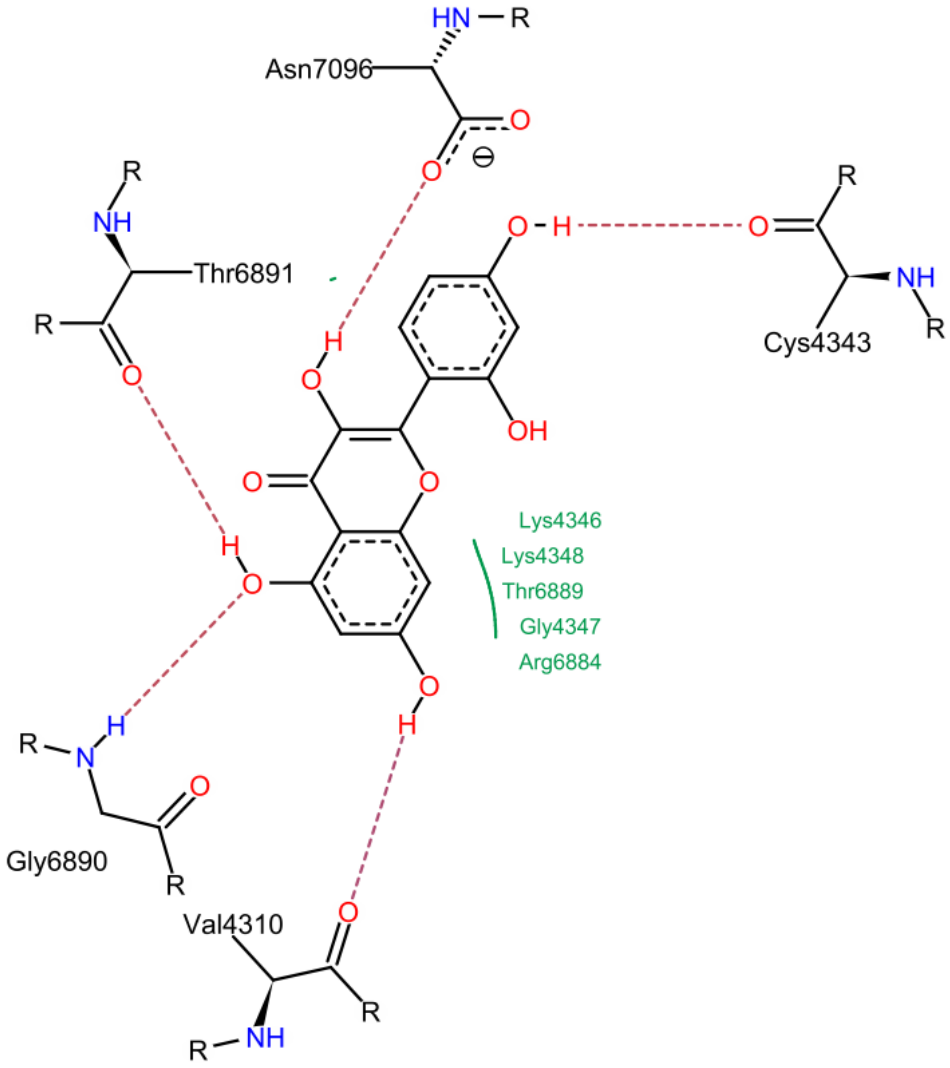


Figure 1: Binding pattern of **Morin** with NSP10 - NSP16 complex protein

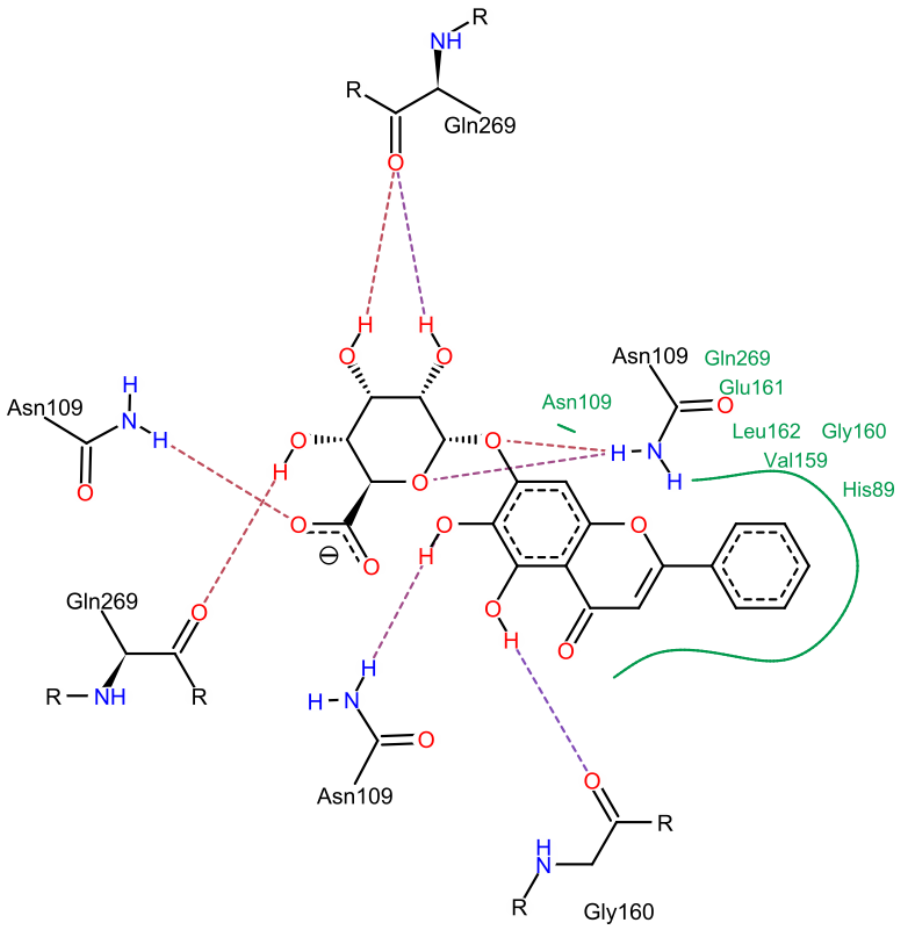


Figure 2: Binding pattern of **Baicalin** with papain-like protease

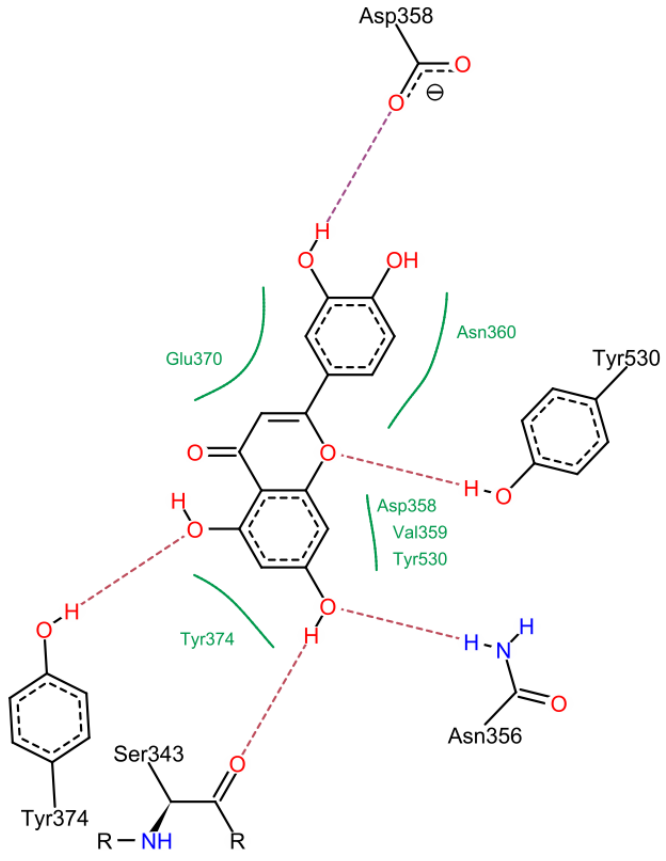


Figure 3: Binding pattern of **Luteolin** with RNA-dependent RNA polymerase

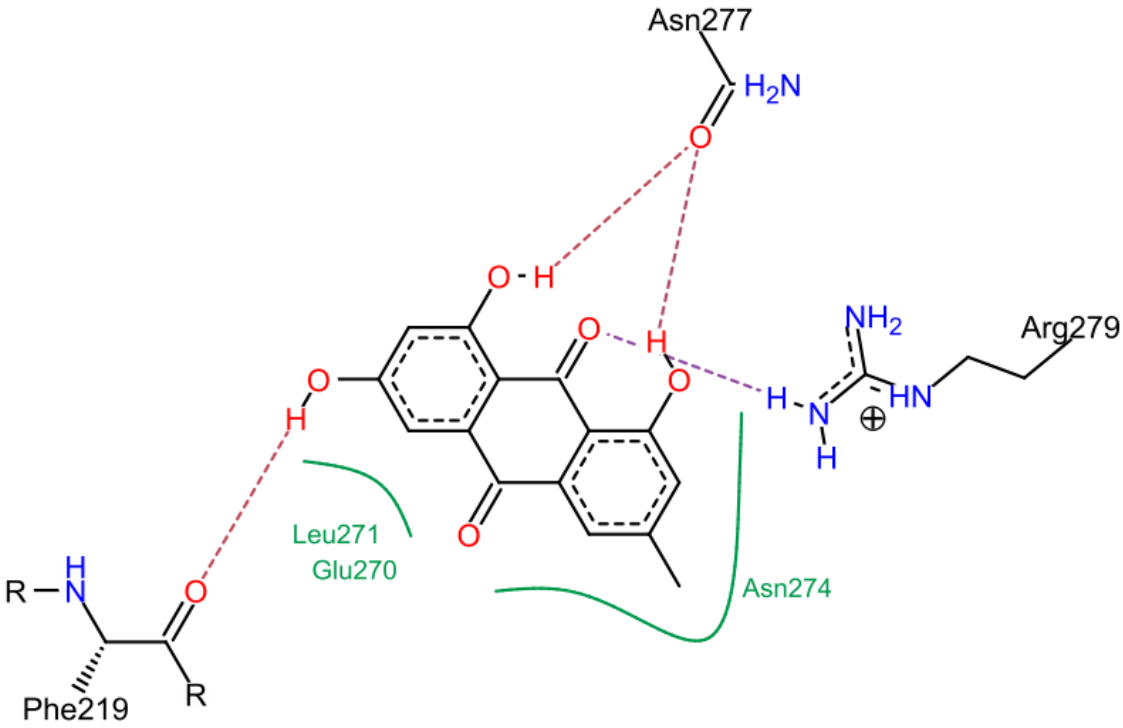


Figure 4: Binding pattern of **Emodin** with COVID-19 main protease

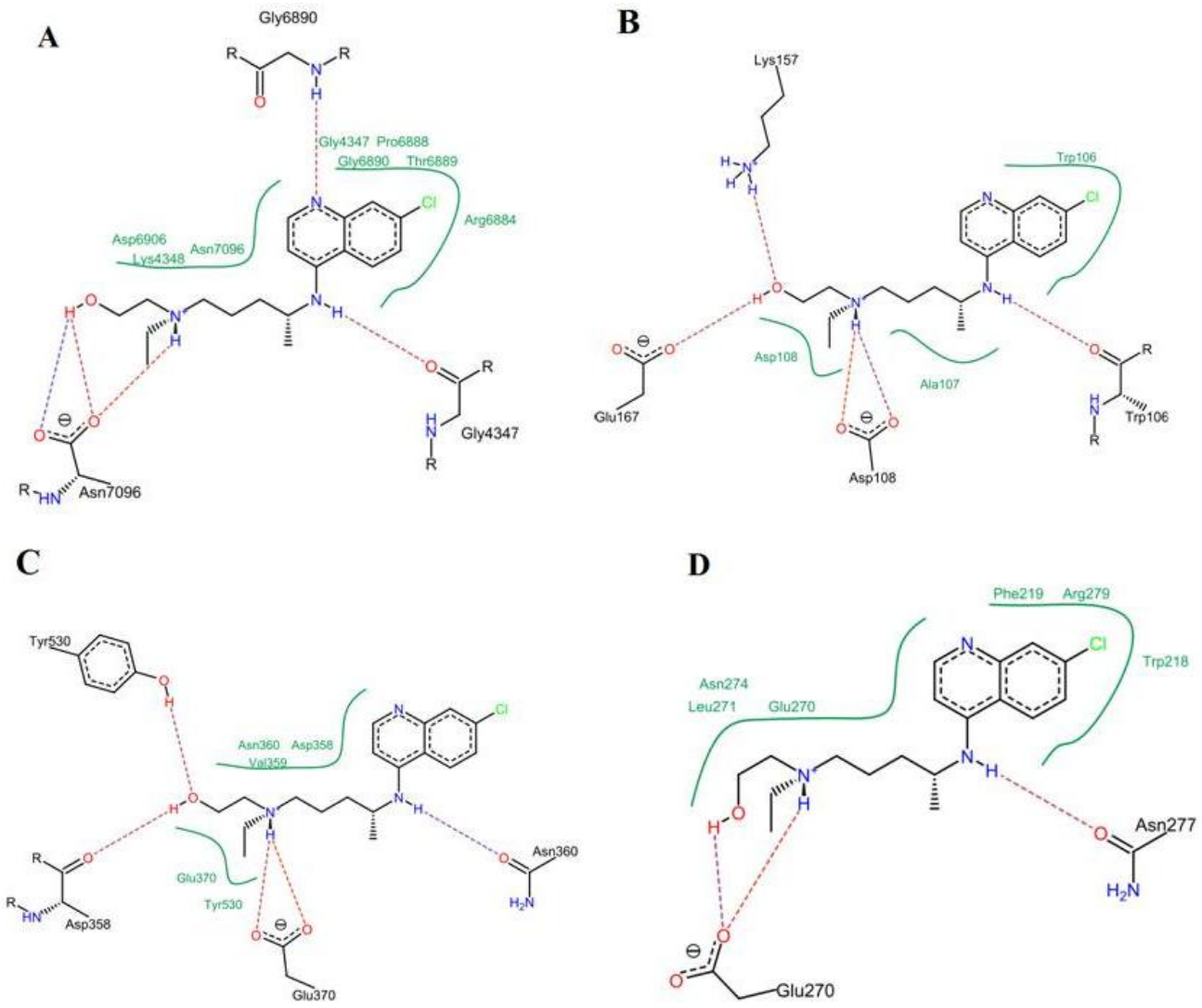


Figure 5: Binding pattern of **Hydroxychloroquine** with **A**: NSP10 - NSP16 Complex, **B**: papain-like protease, **C**: RNA-dependent RNA polymerase, **D**: main protease

Discussions

While considering better ligands, the least score in docking was preferred as it indicates more stability in binding[24]. The interactions of phytochemicals and control with targets were screened based on hydrogen bonding based prediction[25]. Docking score of **Hydroxychloroquine (control)**, with NSP10 - NSP16 Complex, Papain-like protease, RNA-dependent RNA polymerase and COVID-19 main protease is -16.8433 Kcal/mol, -17.4223 Kcal/mol, -15.7864 Kcal/mol and -6.7979 Kcal/mol respectively and forms four hydrogen bonds with NSP10 - NSP16 Complex, five hydrogen bonds with Papain-like protease, five hydrogen bonds with RNA-dependent RNA polymerase and forms three hydrogen bonds with COVID-19 main protease.

Some phytochemicals exhibit better binding efficacy with NSP10 - NSP16 Complex protein, some shows strong bonding with Papain-like protease, some interact strongly with RNA-dependent RNA polymerase and some others forms bond with COVID-19 main protease.

The flavone, **morin** isolated from *Prunus dulcis, Chlorophora tinctoria, Psidium guajava* and other plants shows better bonding with the target NSP10 - NSP16 Complex protein with a docking score of -26.8255 Kcal/mol and forms five hydrogen bonds.

Baicalin a flavonoid obtained from roots of the plant *Scutellaria baicalensis* has the highest docking score (-34.3309 Kcal/mol) with the receptor papain-like protease among all the phytochemicals and control also forms seven hydrogen bonds with the receptor.

The flavone, **luteolin** isolated from *Matricaria inodora* L. plant has more binding efficacy with the target RNA-dependent RNA polymerase with a docking score of -24.3635 Kcal/mol and forms five hydrogen bonds with the receptor.

Emodin a polyphenol found in the roots, leaves, and bark of several plants, including *Aloe barbadensis, Rhamnus pushiana, Rheum officinale, Cassia angustifolia, Polygonum multiflorum, Polygonum cuspidatum, Psychotria camponutans* etc. exhibit strong bonding with COVID-19 main protease receptor with docking score of -20.0202 Kcal/mol and forms three hydrogen bonds.

From predicted ADME parameters and drug like nature of phytochemicals obtained from SwissADME web tool, it was found that some of the compounds do not obey the Lipinski's rule and show alert/warning in medicinal chemistry but being natural products these does not matter a lot.

Among the four best binding compounds with all targets, **morin** neither violate any rules nor shows any alert/ warning also it binds with all the targets significantly.

Hydroxychloroquine (control) forms hydrogen bonds with GLY4347, GLY6890 and ASN7096 residues of NSP10 - NSP16 Complex protein similarly **morin** forms hydrogen bonds with GLY6890, ASN7096, VAL4310, CYS4343 and THR6891 residues of the same receptor. Both form hydrogen bonds with GLY6890 and ASN7096 residues. Similar pattern was observed with other targets also.

The nsp10/nsp16 protein also known as RNA methyltransferase or MTase is a complex of two critical proteins bound together and the association makes the complex a functional protein. These proteins modify the genetic material of the virus to make it look more like the host (human) cell RNA and allow the virus to hide from the cells, giving it time to multiply. The nsp10/nsp16 protein is a key target because it is absolutely essential for the virus to replicate. If a drug can be developed to inhibit nsp10/nsp16, the immune system should be able to identify the

virus and eliminate it earlier[9], since morin interacts strongly with this target than other phytochemicals and control therefore it may inhibit nsp10/nsp16 protein and thus able to eradicate the virus.

Angiotensin converting enzyme 2 (ACE2) is the major cell receptor of SARS-CoV and SARS-CoV-2. It plays a key role in the entrance of the virus into the cell to produce the final infection[26]; interestingly **morin** has angiotensin converting enzyme inhibition activity also[27].

Morin shows stable bonding pattern with all four targets in compare to other phytochemicals and control as it shows least score in docking, forms maximum number of hydrogen bonds with the active residues of the receptors, therefore **morin** have potentiality to be a drug candidate against Covid-19.

Conclusion

Based on present observation of docking results, ADME parameters and drug like nature, we suggest that **morin** may be a potent new drug candidate against Covid-19. However, further studies are required to validate the same in vivo or in vitro.

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Conflict of Interest Statement: The authors declare no conflict of interests.

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