MOLECULAR DOCKING AND IN-SILICO ADMET ANALYSIS OF POTENTIAL ANTIVIRAL COMPOUNDS FROM *Calophyllum inophyllum* L. AND *Selaginella bryopteris* L. AGAINST COVID-19 MAIN PROTEASE

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ABSTRACT

The SARS-COV-2 produced the severe acute respiratory disorders;(Coronavirus 2019[COVID -19] which is responsible for the global pandemic. Despite extensive research, there are still no specific drugs or vaccines to combat SARS-COV-2 infection. Amentoflavone compounds and its four derivatives (Isochamaejasmin ,Sikokianin B, Wikstaiwanone B ,Wikstaiwanone A) were selected from Calophyllum inophyllum and Selaginella bryopteris. Five plant based anti viral compounds have been selected to examine the inhibitory profiles Via Molecular docking and ADMET analysis by using iGEMDCK Software and ADMETlab2.0 Respectively, for the evaluation against Covid-19 Main protease. This study results have shown very good interaction of plant compounds against the drug targets and H bonds have also formed to enhance the binding complex stability. Among the five compounds, higher binding value compounds have rejected, these compounds are not acceptable for Lipinski's rule of five, therefore there are risk factors for the intake of these antiviral compounds.From this is study we can conclude that these compounds cannot be consumed.

Keywords: COVID-19; SARS-COV-2; Main Protease; Molecular Docking; Selaginella bryopteris ; Calophyllum inophyllum , iGEMDOCK,ADMETlab 2.0.

1. INTRODUCTION

The coronavirus (CoV) has gotten a lot of attention recently, especially since its virulence characteristics have changed to allow for human infection. Six CoV strains cause common cold symptoms, while two SARS strains and two Middle East respiratory syndrome strains cause more severe to fatal infections [5].The SARS-CoV-2 produced severe acute respiratory disorders (coronavirus disease 2019 [COVID-19]); which is responsible for the global pandemic and caused 3.6 Crore (worldwide) and 4.71 Lakh (India) mortality in confirmed cases.

The advancement of COVID-19 therapies has demonstrated great potential, but they are still inconclusive. Vaccine development began, with some promising results.Furthermore, repurposing medications like Remdesivir (REM) or Chloroquine are thought to have a positive impact on the recovery of COVID-19 patients .The researchers also looked at the metabolites of therapeutic plants. By offering a drift for synthetic or semi-synthetic antiviral drugs, natural

materials give remarkable structure and complexity for therapeutic discovery. As previously stated, several phytochemicals acted on the major virulence proteins. In silico studies of various promising Indian and Chinese medicinal plants for COVID-19 treatment were presented in specific. Plant metabolites are promising in the discovery of COVID-19 compounds in these studies.Coronavirus main protease is the best characterized drug target,with no known human protease having the same cleavage pattern,so its inhibition leads to specific blockade of viral replication[6].

The Indian Traditional System of Medicine has been one of the world's oldest medical systems, and it has contributed significantly in providing health care to human civilization from its origin. Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (AYUSH) are the only acknowledged traditional medicinal systems in India. These systems are founded on particular medical philosophies and provide a means of reaching a healthy lifestyle with traditional and established beliefs on the avoidance of illnesses and the promotion of health. The primary therapy strategy of all these systems is integrative and the pharmacological methods are based on natural products of plants, animals, or mineral origin. As a result, there is renewed interest in AYUSH systems, which have previously aided the nation through pandemics such as plague, cholera, and Spanish flu.

In silico (usage of computer modeling hypothetically) and reusing more existing FDA authorized medications could increase this strategy to new drug discovery against COVID-19 .Amentoflavone is a polyphenolic bi-flavonoid present in plants that has a wide range of bioactivities, including antiviral, anti-inflammatory, anti-cancer, anti-diabetic, anti-oxidant, and anti-microbial effects [2].Other famous amentoflavone-containing plants used in Indian traditional medicine include *Selaginella bryopteris* and *Calophyllum* inophyllum[3].

Amentoflavone has been shown to have anti-inflammatory, antioxidative, and vasoprotective properties in studies[12].Scavengingg actions using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), superoxide, and hydroxyl radicals revealed that it has high antioxidant activity (19.2%–75.5%)[6]. It inhibited lipopolysaccharide-induced nitric oxide (NO), reactive oxygen species (ROS), and malondialdehyde (MDA) in a rat astrocytoma cell line; NO, prostaglandin E-2 (PGE-2), nuclear translocation of c-Fos in RAW 264.7 cells; and TNF-a in a human monocytic leukemia cell line, with no other effects on the cells. It decreased the prevalence of IL-6, TNF-a, IL-1b, and PGE2 in human peripheral blood mononuclear cells, inhibiting the oxidative burst of neutrophils and disruption to human erythrocyte membranes generated by phytohemagglutinin.

We examined compounds that target the critical entry mechanism used by SARS-CoV-2 (covid-19) during viral penetration of host cells to find compounds with the potential to act against SARS-CoV-2. We concentrated on chemicals that were found to interact with the SARS-CoV-2 main protease preventing the viral payload from entering the host cytoplasm. To block viral and host cell interactions, we chose drugs that predominantly target the main protease.

We assessed the potential of certain bioactive derivatives of Amentoflavone such as Isochamaejasmin, Wikstaiwanone A, Wikstaiwanone B,Sikokianin B as therapeutic agents against COVID-19 in this paper, based on a thorough examination of the literature. To develop

efficient antiviral medications from medicinal plants for COVID-19 therapy, more research is needed to clinically confirm the findings of this review, either in vitro or in vivo [12].

2.MATERIALS AND METHODS

2.1 SELECTION OF ANTIVIRAL COMPOUNDS FROM MEDICINAL PLANTS

Amentoflavone composites and its four derivations (Isochamaejasmin, Sikokianin B, Wikstaiwanone B, Wikstaiwanone A) were named from *Calophyllum inophyllum* and *Selaginella bryopteris*.

2.2 PROTEIN PREPERATION

The protein needed for the docking studies has been recaptured from the Protein Data Bank at1.2 and1.7 Ǻ root mean square diversions (RMSD) resolution which represents a three-dimensional structure of target Demitasse structure of the Covid- 19 main protease (PDB ID 6LU7)

2.3 LIGAND PREPERATION

The ligand motes for the docking process are prepared from the composites attained from *Selaginella bryopteris* and *Calophyllum inophyllum* source. The composites were attained from the PubChem database. The structure of the composites was downloaded in(. sdf) format and they were converted into(. Pdb) format by using openbabel software searching for tautomers and steric isomers and figure minimization of ligands.

2.4 DOCKING MODULE

Docking software iGEMDOCK was used to dock the protein Demitasse structure of the Covid-19 main protease(PDB ID 6LU7) of the nimbus contagion with the medicine composites. iGEMDOCK is an intertwined virtual webbing(VS) terrain from medications throughpost-screening analysis with pharmacological relations. iGEMDOCK provides interactive interfaces to prepare both the list point of the target protein and the webbing emulsion library. Each emulsion in the library is also docked into the list point by using the in- house docking tool iGEMDOCK. Latterly, iGEMDOCK generates protein- emulsion commerce biographies of electrostatic(E), hydrogen- cling(H), and Van der Waal's(V) relations. Grounded on these biographies and emulsion structures, iGEMDOCK infers the pharmacological relations and clusters the webbing composites for thepost-screening analysis. Eventually, iGEMDOCK species and visualizes the webbing composites by combining the pharmacological relations and energy- grounded scoring function of iGEMDOCK.

2.5 MEDIUM OF DOCKING

Docking was performed by iGEMDOCK molecular docking software. During Docking, at first the motes were prepared and bonds, bond orders, unequivocal hydrogen's, charges, flexible torsions were assigned to both the protein and ligands. From the Docking, wizard ligands were named and the scoring function used was iGEMDOCKscore.However, the hydrogen bond energy donation to the Docking score is assigned a penalty grounded on the diversions from the ideal cling angle, If hydrogen cling is possible. This option can significantly reduce the number of doubtful hydrogen bonds and also internal electrostatic commerce; internal hydrogen bond sp2- sp2 torsions are calculated from the disguise by enabling the ligand evaluation terms. The hunt algorithm is taken as iGEMDOCK and figures

of runs taken are 10 and maximum relations were 2000 with population size 200 and with an energy threshold of 100 also at each step least ‘ min ’ torsions/ restatements/ reels are tested and the one giving smallest energy is chosen. If the energy is positive(i.e. because of a clash or an inimical electrostatic commerce), also fresh ‘ uttermost ’ positions will betested.However, an redundant penalty term(the Energy penalty) is added to the scoring function, If the disguise being docked is near to one of the ligands in the list than specified by the Root Mean Square Divagation(RMSD) threshold. This ensures a lesser diversity of the returned results since the docking machine will concentrate its hunt on acts different from earlier acts plant. The energy penalty was set to 100, RMSD threshold was2.00 and RMSD computation by snippet ID(fast) were set. Docking was conducted between Protein and Asset which results in binding affections in kcal/ spook and docking run time. The emulsion which gives smallest binding energy is chosen as the stylish asset.

2.6 ADMET ANALYSIS OF AMENTOFLAVONE AND ITS DERIVATIVES

ADMET Screening is the batch mode of evaluation, designed for the vaticination of molecular datasets. SMILES strings and SDF/ TXT formatted lines are supported molecular submission approaches. This module is suitable for the evaluation of empirically designed or visually screened motes before chemical conflation and biochemical assays, which allows scientists to more concentrate their trials on the most promising composites.

2.7 Exhaustively enhanced ADMET biographies

Undesirable pharmacokinetics and toxin of seeker composites are the main reasons for the failure of medicine development, and it has been extensively honored that immersion, distribution, metabolism, excretion and toxin(ADMET) of chemicals should be estimated as early as possible. ADMETlab2.0 is an enhanced interpretation of the extensively used ADMETlab for systematical evaluation of ADMET parcels, as well as some physicochemical parcels and medicinal chemistry benevolence. With significant updates to functional modules, prophetic models, explanations, and the stoner interface, ADMETlab2.0 has lesser capacity to help medicinal druggists in accelerating the medicine exploration and development process. These results suggest that opting composites with pharmacophoric parcels(Lipinski’s rule of five) and performing the molecular docking webbing to search implicit impediments are intriguing strategies that could be used for high outturn wireworks aiming to descry new composites with desirable naturalactivity.Various parameters have been prognosticated to elect the potent asset against the Covid viral protein, ADMETlab2.0 is available for the vaticination of every important aspect of molecular quality, covering major endpoints that medicinal druggists would be interested in. Some toxicophore rules, toxin pathways, and some medicinal chemistry measures of this platform are unique among the tools of this kind ADMET lab.2 has also been used for assessing ADMET parameters vaticination. ADMETlab2.0 which significantly enhanced the functionality of its precursor. The new webserver provides the druggies easy access to comprehensive, accurate and effective vaticination of the ADMET biographies for chemicals, including immersion, distribution, metabolism, excretion and toxin parcels, as well as some important physicochemical and medicinal chemistry parcels.

ADMETlab2.0 provides medicinal druggists a comprehensive, accurate, effective, and stoner friendly service for ADMET evaluation.

3.RESULT AND DISCUSSION

Amentoflavone compounds and its four derivatives (Isochamaejasmin ,Sikokianin B, Wikstaiwanone B ,Wikstaiwanone A) were selected from *Calophyllum inophyllum* and *Selaginella bryopteris.* The main protease target protein (7BRP) was docked against Amentoflavone compounds and its four derivatives. Amentoflavone has four hydrogen bonds with binding energy-74.17 ,Isochamaejasmin has three hydrogen bonds with binding energy -81.75,Sikokianin B and Wikstaiwanone B has two hydrogen bonds with binding energy -40.69 and -16.7 respectively and Wikstaiwanone A has one hydrogen bond with binding energy -50.91. (Table 1; Plate). All the five components were found to be best hits with the higher binding affinities against covid-19main protease target but none of them shows positive results for ADMET analysis. Binding energies were tabulated (table1) with number of hydrogen bonds(Hbonds), amino acids involved in Hbonds and drug likeliness of the compounds. Binding energies are one of the important criterias for selecting a potent inhibitor against the selected drug target to map the inhibition efficiency. Compounds are ranked according their binding energy, higher the binding energy indicated higher the binding affinity of protein ligand complex[4]. Another important criteria is Hbonds formation, based on the hbonds the binding complex are considered to be more interactive and strong. Hydrogen bonds play a major role in the stabilization of protein-ligand complexes [11].

Antiviral activity of the plants highlighted in This study whose phytochemicals are predicted to have inhibitory effect on Covid-19 main protease target have proven antiviral role on other human pathogenic viruses. Antiviral activity of Selaginella and Amentoflavone against influenza A and B viruses, Herpes simplex virus (HSV)-1 and HSV-2 and moderate activity against Human immunodeficiency virus (HIV)-1 reverse transcriptase (RT) [10].*Calophyllum inophyllum* was reported to have antiviral effect against Human immunodeficiency Virus (HIV) reverse transcriptase(RT) [1]. Likewise Inhibitory activities against two prime enzymes of HIV which are HIV-1 protease (HIV-PR) and HIV-1 integrase (HIV-IN)[9].

Amentoflavone exhibited its anti-dengue potential in a screening experiment, which may be mediated by inhibiting Dengue virus NS5 RNA-dependent RNA polymerase Amentoflavone was proved as the most active one to inhibit severe acute respiratory syndrome coronavirus (SARS-CoA) with IC50 value of 8.3 µM. The effect was concluded relative to the inhibition of chymotrypsin-like protease (3CLpro) . Amentoflavone was also found to decrease Coxsackievirus B3 (CVB3) replication by inhibiting fatty acid synthase (FAS) expression . Moreover, in cases of human immunodeficiency virus (HIV) and respiratory syncytial virus (RSV), amentoflavone showed good performance with IC50 values of 119 µM and 5.5 µg/mL respectively[12].

3.1 ADMET ANALYSIS

The Lipinski's rule of five is the rule of thumb to evaluate the drug-likeness and to determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. Ro5 depends on four simple physiochemical parameter ranges: the molecular weight (MW), which should be less than 500 g/mol, lipophilicity (Log P) less than 5, and number of hydrogen bond donors and acceptors less than 5 and 10, respectively, as seen for 90% of orally functional drugs that have obtained phase II clinical status. These parameters are connected with intestinal permeability and aqueous solubility and determine the first step of oral bioavailability. These rules explain molecular properties valuable for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). If a ligand fails to fulfill the parameters of Ro5, then it is highly probable that it will cause trouble if ingested (Mendis et al.,2011) ADME properties are important to understand the pharmacokinetics and physio-chemical properties of phytochemicals which further provides insight on drug design and formulation research(Saranya et al., 2021) .But in this work none of them shown positive result for Lipsinki's rule of five therefore all the phytochemical and its derivatives are rejected for Lipsinki's rule of five.

TABLE-I

Table contains binding energy ,Number of H-bonds ,Amimoacid -H bonds and Drug Likeness of the phytochemicals.

Sl.No	COMPOUNDS	BINDING ENERGY	NUMBER OF H-BONDS	AA -H BONDS	DRUG LIKENESS
1	AMENTOFLAVONE	-74.17	**4**	CYS 145 SER 144 GLU166 GLY 170	REJECTED
2	ISOCHAMAEJASMIN	**-81.75**	3	GLU 166 GLN 189 ALA 2	REJECTED
3	SIKOKIANIN B	-40.69	2	THR 169 ALA 2	REJECTED
4	WIKSTAIWANONE A	-50.91	1	ALA 191	REJECTED
5	WIKSTAIWANONE B	-16.7	2	CYC 85 ALA 173	REJECTED

Table-I shows that Amentoflavone has four hydrogen bonds with binding energy-74.17, Isochamaejasmin has three hydrogen bonds with binding energy -81.75, Sikokianin B and Wikstaiwanone B has two hydrogen bonds with binding energy -40.69 and -16.7 respectively and Wikstaiwanone A has one hydrogen bond with binding energy -50.91.

PLATE- I

Covid-19 Main Protease V/S Amentoflavone

Four hydrogen bonds have been formed towards the crystal structure of COVID-19 main protease with GLY 170,GLU 166,SER 144 and CYS 144.

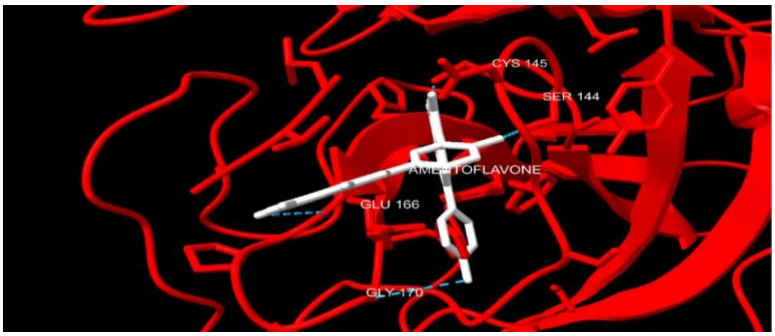


PLATE-II

Covid-19Main Protease V/S Isochamaejasmin

Three hydrogen bonds have been formed between the amino acids of crystal structure of COVID-19 main protease. The amino acids involved in hydrogen bonding are GLN 189,GLU 166 and ALA 2.

PLATE-III

Covid-19Main Protease V/S Sikokianin B

Two hydrogen bonds have been formed between the aminoacids of crystal structure of COVID-19 main protease.The aminoacids involved in hydrogen bonding areTHR169 and ALA 2.

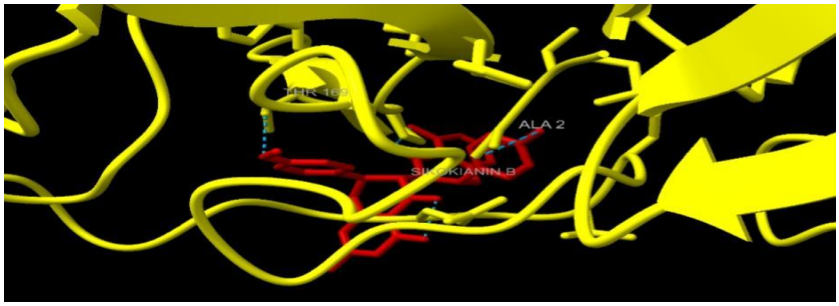


PLATE-IV

Covid-19 Main Protease V/S wikstaiwanone A

One hydrogen bonds has been formed between the amino acids of crystal structure of Covid -19 main protease. The amino acid involved in hydrogen bonding is ALA 191.

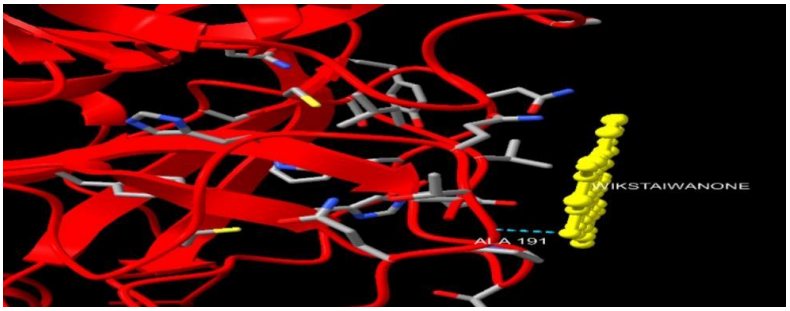
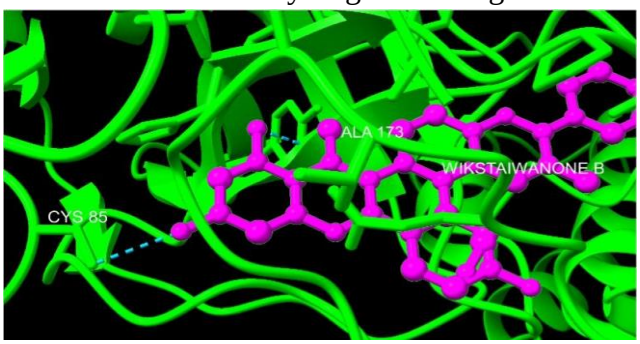


PLATE-VI

Covid-19MainProteaseV/SwikstaiwanoneB

Two hydrogen bonds have been formed between the amino acids of crystal structure ofCOVID-19 main protease. The amino acids involved in hydrogen bonding are CYS 85 and ALA 173 .



ADMET ANALYSIS

TABLE-II

Medicinal Chemistry

Property	Value	Decision	Comment
Lipinski Rule	Rejected	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.

Property	Value	Decision	Comment
Caco-2 Permeability	-5.263	🔴	Optimal: higher than -5.15 Log unit
MDCK Permeability	8e-06	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.02	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.016	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.672	🟡	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

Distribution

Property	Value	Decision	Comment
PPB	96.91%	🔴	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.479	🟢	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.001	🟢	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	4.674%	🔴	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

Excretion

Property	Value	Decision	Comment
CL	3.819	🔴	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.638	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.096	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.146	🟢	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.988	🔴	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.258	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.068	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.836	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.902	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.

ISOCHAMAEJASMIN

TABLE-III

Medicinal Chemistry

Property	Value	Decision	Comment
Lipinski Rule	Rejected	🔴	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	🟢	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	🔴	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	🔴	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.

Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-6.011	🔴	Optimal: higher than -5.15 Log unit
MDCK Permeability	6e-06	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.082	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.0	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.655	🟡	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

Distribution

Property	Value	Decision	Comment
PPB	97.94%	🔴	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.627	🟢	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.002	🟢	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	2.452%	🔴	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

Excretion

Property	Value	Decision	Comment
CL	8.482	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.298	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

Toxicity

Property	Value	Decision
Lipsinki Rule	Rejected	
Pfizer rule	Accepted	
GSK Rule	Rejected	
Golden Triangle	Rejected	

Property	Value	Decision	Comment
hERG Blockers	0.044		■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.06		■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.968		■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.18		■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.947		■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.066		■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.891		■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.

SIKOKIANIN B

TABLE-IV

Medicinal Chemistry

Absorption

Property	Value	Decision
CaCo-2 Permeability	-5.860	
MDCK Permeability	6.7e-0.6	
Pgp-inhibitor	-----	
Pgp-Substrate	-----	
HIA	+	

Distribution

Property	Value	Decision
PPB	98.279%	
VD	0.668	
FU	1.975%	

Excretion

Property	Value	Decision
CL	6.447	
T ½	0.183	-

Toxicity

Property	value	Decision
Herg Blockers	---	
H-HT	---	
DILI	+++	
AMES Toxicity	--	
Rat oral Acute Toxicity	+++	

FDAMDD	--	
Skin sensitization	++	
Carcinogenicity	---	
Respiratory Toxicity	---	
Eye Irritation	++	

WIKSTAIWANONE A

TABLE-V

Medicinal Chemistry

Property	Value	Decision	Comment
Lipinski Rule	Rejected	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.

Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-6.308	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	5e-06	●	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.031	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.003	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.274	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

Distribution

Property	Value	Decision	Comment
PPB	98.86%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.354	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.003	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	2.072%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

Excretion

Property	Value	Decision	Comment
CL	5.012	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.644	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

TOXICITY

Property	Value	Decision	Comment
hERG Blockers	0.078	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.456	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.985	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.751	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.182	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.061	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.587	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.

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TABLE-VI

Medicinal Chemistry

Property	Value	Decision	Comment
Lipinski Rule	Rejected	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.

Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-6.082	🔴	Optimal: higher than -5.15 Log unit
MDCK Permeability	9e-06	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.06	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.0	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.009	🟢	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

Distribution

Property	Value	Decision	Comment
PPB	100.6%	🔴	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.557	🟢	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.005	🟢	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	0.862%	🔴	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

Excretion

Property	Value	Decision	Comment
CL	6.823	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.348	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.141	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.088	🟢	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.948	🔴	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.37	🟡	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.753	🔴	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.885	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.929	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.

4. CONCLUSION

Five plant based antiviral compounds have been selected to examine the inhibitory profiles evaluation against the drug targets and H bonds have also formed to enhance the binding complex stability. Among the five compounds, higher binding value compounds have rejected. These compounds are not acceptable for Lipsinki Rule of five.Therefore these antiviral compounds are not suitable for drug preparation against COVID-19.

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