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In Silico Molecular Docking of Phytochemical Compounds of *Ocimum bacilicum* Against Mutated SARS-CoV-2 Virus

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Abstract: The COVID-19 pandemic caused by the SARS-CoV-2 virus, which originated in Wuhan, China in 2019, spread globally resulting in millions of confirmed cases and deaths. To address this urgent need, the researchers explored the potential of natural remedies as an alternative to current existing synthetic drugs. In this study, the researchers virtually screened and docked the phytochemicals present in *Ocimum basilicum* against the targets of SARS-CoV-2. All the five phytocompounds (Apigenin, Xanthmicrol, Eriodictyol, Kaempferol and Luteolin) obeyed Lipinski rule of five. Among the selected ligand molecule, the ADME property of Eriodictyol was good. Further toxicity analysis revealed that there was no indication of hepatotoxicity, immunotoxicity, mutagenecity and cytotoxicity in Xanthomicrol, Eriodictyol and Kaempferol. The selected ligand molecules were subjected to Molecular Docking using AutoDockVina. Compared to other drug candidates, Eriodictyol showed better interaction against SARS-CoV-2 targets proteins COVID-19 main protease (PDB ID: 6LU7), SARS-CoV-2 RNA-dependent RNA polymerase (PDB ID:7BTF), and Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2) (PDB ID:1R4L) with binding energy of -7.7, -7.2 and -8.8 Kcal/mol. Eriodictyol as a ACE-2 inhibitor, could inhibit ACE-2 by altering its structural composition or by affecting glycosylation, which prevents ACE-2 from arriving to the surface and blocking the virus's ability to enter the host cell. Overall, the study suggests that natural remedies, such as the Eriodictyol present in *Ocimum basilicum*, may provide a potential alternative approach to the treatment of COVID-19. Further research is needed to explore the efficacy of these compounds and their potential as therapeutic agents.

Keywords: SARS-CoV-2, *Ocimum basilicum*, Eriodictyol, ACE-2 receptor, COVID M^{PRO}, SARS-CoV-2 RNA-dependent, RNA polymerase, Molecular Docking

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Introduction

A new coronavirus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is now responsible for the extremely infectious sickness known as COVID-19 *(*Zhu *et al*., 2020).

This viral infection outbreak started as a result of a zoonotic transmission from a seafood market in Wuhan, China (Mackenzie and Smith, 2020). The SARS-CoV-2 virus that causes COVID-19 was initially thought to be an viral epidemic in China, but within a few weeks, the World Health Organization (WHO) proclaimed it to be a worldwide pandemic in March, 2020 (Cucinotta and Vanelli, 2020). Globally, 75, 62, 91, 327 confirmed cases of COVID-19, including 68,41,640 deaths, reported by WHO on February 2023. As of February 2023, a total of 13,19,57,77,466 vaccine doses have been administered (https://covid19.who.int/).

SARS-CoV-2 is a member of the *Coronaviridae* family of viruses, which belongs to the genus ß-coronavirus (Gorbalenya *et al.*, 2020; Machhi *et al.*, 2020). This family includes enclosed and positive-sense, single-stranded RNA viruses that are linear in nature (Pal *et al.,* 2020). Coronaviruses have the biggest genomes among RNA viruses (Mousavizadeh and Ghasemi, 2021). All other SARS-CoV-2 isolates have genomes that are around 30 kb in size, which is typical of coronaviruses (Mackenzie and Smith, 2020; Bar-On *et al.*, 2020), with the exception of the early isolate from Wuhan, which had a genome of 29,903 nucleotides. The Omicron variety has at least 32 mutations, which is greater than the Delta virus strain, which has a total of 15 mutations.

More than 300 Covid-19 vaccines were reported under preclinical or clinical research as of May 6, 2022, according to the WHO. The WHO has approved the use of ten Covid-19 vaccinations, representing eight different vaccine formulations worldwide. These vaccines are based on four different vaccine platforms: adenovirus vector-based vaccines (AstraZeneca's Vaxzevria and Covishield ChAdOx1 and Johnson and Johnson-Ad26.COV2.S), inactivated virus vaccines (Sinopharm's Covilo, Sinovac's CoronaVac, and Bharat Biotech's Covaxin), and messenger RNA (mRNA) vaccines [(Moderna's SpikevaxMrna-1273, Pfizer (BNT162b2)] and adjuvant protein vaccine (Novavax's Nuvaxovid and Covavax NVX-Co V2373).

For this current deadly infectious disease, it is imperative to develop drugs or a vaccine as soon as possible. Unfortunately, there are currently no FDA-approved medications on the market, and developing new therapeutic molecules and vaccines is still expensive, time-consuming, and fraught with risk (Abd El-Aziz and Stockand, 2020). With this in mind, it is essential to employ other methods of conflict resolution. Due to their safer, more affordable, and lower toxicity profiles, medicinal plants have been the most widely used therapeutic alternatives against many viral infections from ancient times (Ansari *et al.,* 2020).

The genus *Ocimum*, which has more than 150 species, is widely spread and thrives in moderate climates worldwide (Jirovetz *et al.*, 2001; Manosroi *et al.*, 2006; Mirdha *et al.*, 2007). According to (Sartoratto *et al.*, 2004; Chiang *et al.*, 2005), it has also been used in traditional medicine to treat a variety of illnesses, including respiratory and gastric disorders. The possible effects of basil on bacteria, fungi, and viruses have all been proved (Suppakul *et al.*, 2003; Sartoratto *et al.*, 2004; Pozzatti *et al.*, 2008;). When it comes to phytochemicals, phenolic compounds such as flavonoids found in a variety of plants and foods have been linked to defensive mechanisms against viral diseases such the Poliovirus type 2, Hepatitis B and C virus, Adenoviruses, Influenza virus, and Human Immunodeficiency Virus (Zakaryan *et al.*, 2017). In the current study phytocompounds (Apigenin, Xanthomicrol, Eriodictyol, Kaempferol and Luteolin) of *Ocimum basilicum* were virtually screened and docked against targets of SARS-CoV-2. The best docked compound could be a potential inhibitor of targets which has been discussed in the present study.

Materials and Methods

Bioinformatics databases and tools such as PubChem, National Library for biotechnology Information (NCBI), Marvin Sketch (ChemAxon), Swiss ADME, PreADME, EPI-Suite, Pass online,

Gusar, Auto dock vina for docking, Chimera and Desmond (Academic Version) were used to investigate *In silico* study of *Ocimum basilicum* against targets of SARS COVID-19.

Ligand selection and preparation:

Online resources including Dr. Duke's phytochemical and ethnobotanical database (https://phytochem.nal.usda.gov/) and IMPPAT (https://cb.imsc.res.in/imppat/) were used to aid with the selection of bioactive phytochemicals of *Ocimum basilicum*. The three-dimensional (3D) structures of the chosen phytochemicals were acquired in Structural Data File (SDF) format from the PubChem database. The National Institute of Health (NIH) maintains the PubChem open-source database, which includes information on chemical structures, IDs, chemical and physical characteristics, biological activities, patents, health and safety information, and toxicity data (Kim *et al.*, 2021). Moreover, Avogadro software used the universal force field (UFF) method to carry out structural optimization. It makes use of frequencies, single-point energies, and information from geometric optimization (Rappé *et al.*, 1992).

Prediction of physiochemical properties:

The physiochemical selection procedure used Lipinski's Rule of Five criteria. This rule was examined using the online Swiss ADME Tool (http://www.swissadme.ch/). Lipinski's rule states that for a compound to be a ligand, it must have certain characteristics, such as H bond acceptors of fewer than 10, H bond donors of fewer than 5, a molecular weight of less than 500, high lipophilicity, a value of Log P of less than 5, and total polar surface area (TPSA) that should not be greater than 140. A compound was not included in the examination if it broke more than two guidelines. The compound's solubility, the drug's lipophilicity (Log P) value and HLB value (Hydrophilic-lipophilic balance number) was assessed using the Marvin sketch programmer.

ADME property prediction of ligands:

To ascertain their impact on the human body, bioavailability and pharmacokinetic features such absorption, distribution, metabolism, and excretion variables were analyzed. The Swiss ADME online web tool was used for the evaluation. The structures of the isolated compounds were converted to their canonical simplified molecular input line-entry systems (SMILEs), and the SMILES of all selected ligands were utilized as input data to estimate *in silico* pharmacokinetic parameters.

Toxicity prediction:

The nature of the drug and its level of toxicity were predicted using a variety of toxicity predictors, including General Unrestricted Structure-Activity Relationships (GUSAR), ECOSAR, and PROTOX. All hazardous model types were thoroughly assessed, including those that predicts environmental toxicity, carcinogenicity, animal toxicity, mutagenicity, and cytotoxicity of cells (Tripathi *et al.*, 2019; Ghannay *et al.*, 2020)

Auto Dock Vina:

Virtual screening is currently developed as a successful concept for separating chemicals for drug development. It was done with PyRx 0.8. (Virtual Screening Tools). One file containing all the drug-like phytochemicals that were obtained from the Protein Data Bank (PDB) database in SDF format. The SDF file was imported into PyRx's open babel, where all of the ligands' energies were then reduced, and then converted to Auto Dock PDBQT format. Moreover, these ligands were evaluated to docking to the 6LU7, IR4L and 6M17 of SARS-COVID 19 virus using Auto Dock Vina in PyRx 0.8 (Trott and Olson, 2010).

Results and Discussion

Selection and preparation of ligands:

The 2D structures of selected compounds from *Ocimum basilicum* were generated using Marvin sketch as shown in Figure 1.

Validation of drug properties:

The physiochemical characteristics of the selected ligand molecules are given in Table 1. The

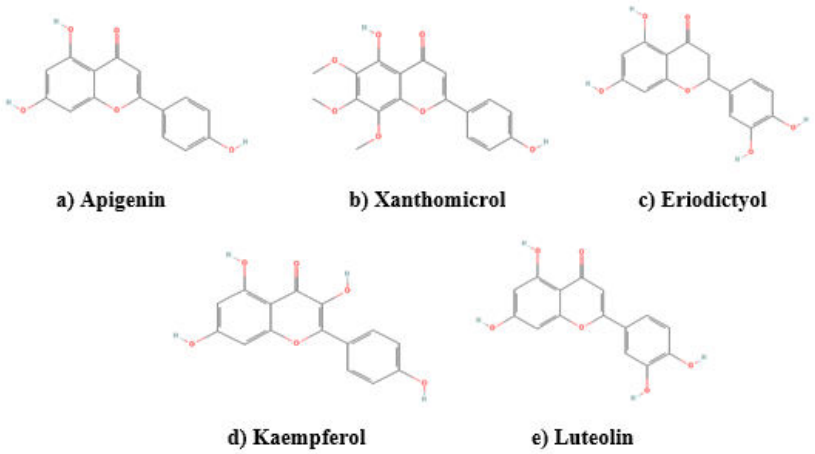

Fig. 1: 2D structure of Screened Ligands.

Table 1: Physiochemical property prediction of ligands

Ligands	Solubility and Liphophilicity							
	Molecular Formula	Molecular mass g/mol	No of H-bond acceptors	No of H-bond donors	Total polar surface Area Å²	Solubility (mg/ml)	Class	Log P
Apigenin	C15H10O5	270.24	5	3	90.90	3.07e-02	Moderately soluble	1.89
Xanthomicrol	C18H16O7	344.32	7	2	98.36	3.17e-02	Moderately soluble	2.99
Eriodictyol	C15H12O6	288.25	6	4	107.22	1.60e-01	Soluble	1.62
Kaempferol	C15H10O6	286.24	6	4	111.13	1.40e-01	Soluble	1.70
Luteolin	C15H10O6	286.24	6	4	111.13	5.63e-02	Soluble	1.86

aforementioned physiochemical property plays a major role in deciding the solubility and lipophilicity of ligand molecule. The drug molecules' capacity for oral absorption or membrane permeability is indicated by these factors, which happen when the drug molecules obey Lipinski's rule of five (Lipinski *et al.*, 2012). If the following conditions are met by the molecule i.e., (a) molecular weight 500; (b) sum of OH and NH hydrogen bond donors >5; (c) sum of O and N hydrogen bond donors >10; and (d) C log P 5, the compound is more likely to have poor absorption. Similar to this, Veber *et al.* (2002) suggested a model for predicting good availability of the drug, which should have (a) <10 rotatable bonds; (b) Polar surface area <140 A² or sum of hydrogen bond donors and acceptors < 12; All of the ligand molecules' molecular weights were within the ideal range of 500 g/mol these low molecular weights revealed that the compounds are expected to be easily diffused, absorbed, or transported through cell membranes. The hydrogen acceptor and the hydrogen bond donors were within the optimal range. Drug design were taken into account the solubility (logS) of organic compounds in water since this parameter frequently has a substantial influence on various ADME-related aspects of medications, such as absorption, distribution, transport, and eventually bioavailability (Hou *et al.*, 2004). The Polar surface areas of all the drug molecules were determined to be less than 140 Å². Among the 5 molecules, the

Kaempferol and Luteolin showed a higher polar surface area of 111.13 $Å^2$ and apigenin showed a minimum polar surface area 90.90 $Å^2$.

Ligands such as Apigenin and Xanthomicrol were found to be moderately soluble, while the drug molecules Eriodictyol, Kaempferol and Luteolin were soluble in water. Since Curcumin was hydrophobic, the neutral solvent cannot dissolve it very well (i.e., Water). But in organic liquids, it dissolves readily (Priyadarsini, 2014). Low solubility, physiochemical instability, restricted bioavailability, rapid metabolism, and poor pharmacokinetics limit the clinical value of native curcumin (Yallapu *et al.*, 2015).All the 5 compounds have good permeability with positive logP values. The fact that all of the medication compounds were lipophilic suggests greater permeability and elimination of compound. In contrast to the two standards (Remdesivir and Azithromycin) with two violations each, the chosen chemicals, such as alkaloids, phytosterols, and flavonoids, comply the RO5 (Abdul-Hammed *et al.*, 2022). According to the ADMET prediction, the only compounds from *Azadirachta indica* that have good pharmacokinetics and toxicity profiles are Azadironic acid, Nimbionone, Nimbionol, and Nimocinol (Adegbola *et al.*, 2021).

The drug molecules in Table 1 satisfy the Lipinski rules of five, indicating that these derivatives have high absorption and penetration and, therefore, theoretically meet the requirements for oral bioavailability. The drug-likeliness of a drug molecule is shown in Table 2. The compounds are suitable for drug absorption owing to the bioavailability score of 0.55.

ADMET property prediction:

The ADME properties of phytochemical compounds of *Ocimum basilicum* such as Apigenin, Xanthomicrol, Eriodictyol, Kaempferol and Luteolin are given in Tables 3 and 4. The first stage of drug discovery can be achieved using a computer-based drug design technique called ADMET analysis (Lipinski, 2001). Blood-brain barrier (BBB), human intestinal absorption (HIA), P-glycoprotein (pGP) substrate/inhibitor, caco-2 permeability, plasma protein binding, cytochrome p450 (CYP450) substrate/inhibitor, inhibition of the human ether-a-go-related gene (hERG), ADME toxicity, carcinogenicity, and biodegradability were all examined in this study. HIA is calculated as the sum of bioavailability and absorption based on the ratio of excretion. The HIA of Apigenin, Xanthomicrol, Eriodictyol, Kaempferol and Luteolin were determined to be 88.122839%, 93.452029%, 77.430116%, 79.439289% and 79.427233%, respectively. HIA percentage between 70-100 % is considered as well absorbed; this shows that all the ligands were easily absorbed by the human intestine.

Xanthomicrol showed 93% HIA the aforementioned physicochemical parameters can be used to estimate the permeability of the caco-2 cell from the structures of drug molecules. Human GI absorption typically ranges from 50 to 100% for substances with Pcaco-2 above 5 x 10(-6) cm/s. This can generally be developed into an oral dosage form (Ren and Lien, 2000). The BBB cannot be crossed by the selected ligand molecules. The blood-brain barrier (BBB) can be crossed by Lupeol, Lupenone, Castasterone, and Remdesivir, and the aqueous solubility (log S) values of the chosen compounds and standards are within the acceptable range of 1 to 5 (Tsaioun and Kates, 2011). The $CaCO_2$ level of the compounds taken in the current study fell within the ideal range, pointing to efficient drug absorption. All the ligand molecules were low permeable with log Kp> -2.5. Except Xanthomicrol, all the other drug molecules were found to be non-substrate to CYP3A4 enzyme. Specifically, Lipinski's RO5, Veber's, Ghosh's, Egan's, and Mugge's herbal compounds each had a high GI absorption, solubility, blood-brain-barrier (BBB) permeability, a decent logP value, and did not break any of the guidelines (Khuntia *et al.*, 2021). All the ligand molecules have the inhibition activity on CYP3A4 enzymes. All the drug molecules have the non-inhibition activity on CYP2C19 enzymes. The compounds were non-substrate to CYP2D6 enzyme; Xanthomicrol,

Table 2: Drug Likeness

Ligands	Lipinski rule of 5	Ghose Rule	Bioavailability score
Apigenin	Yes; 0 violation	Yes; 0 violation	0.55
Xanthomicrol	Yes; 0 violation	Yes; 0 violation	0.55
Eriodictyol	Yes; 0 violation	Yes; 0 violation	0.55
Kaempferol	Yes; 0 violation	Yes; 0 violation	0.55
Luteolin	Yes; 0 violation	Yes; 0 violation	0.55

Table 3: Results of ADME tests adsorption and distribution

Compound Name	ABSORPTION			DISTRIBUTION		
	Human intestinal Absorption	Caco-2 permeability	Log Kp (skin permeation) (cm/s)	P-glycoprotein inhibitor	BBB penetration	Plasma Protein Binding
Apigenin	88.122839	10.5468	-5.80	No	No	97.25
Xanthomicrol	93.452029	9.12274	-6.31	No	No	86.59
Eriodictyol	77.430116	4.5336	-6.62	No	No	100.00
Kaempferol	79.439289	9.57744	-6.70	No	No	89.60
Luteolin	79.427233	4.53973	-6.25	No	No	99.71

Table 4: Results of ADME tests metabolism and excretion

COMPOUND NAME	Metabolism						Excretion	
	CYP3A4 substrate	CYP3A4 inhibition	CYP2C19 inhibition	CYP2D6 substrate	CYP2D6 inhibition	CYP2C9 inhibition	T1/2 (half-life period) (h)	Clearance rate (ml/mi/ kg)
Apigenin	No	Yes	No	No	Yes	No	0.856	7.022
Xanthomicrol	Weakly	Yes	No	No	Yes	Yes	0.734	3.748
Eriodictyol	No	Yes	No	No	No	No	0.856	19.889
Kaempferol	No	Yes	No	No	Yes	No	0.905	6.868
Luteolin	No	Yes	No	No	Yes	No	0.898	8.146

Eriodictyol were analyzed to have non inhibitory and inhibitory activity on CYP2D6 and CYP2C9, respectively.

Among all the five ligands, Xanthomicrol with 3.748 ml/min/kg clearance rate showed low excretion rate meanwhile Eriodictyol with 19.889 ml/min/kg clearance rate showed higher excretion. All five compounds had half-lives that were less than one hour. In agreement with the compound's half-life, the clearance rate was high. 100% of the plasma proteins were bound by Eriodictyol, allowing for efficient interactions. This superfamily of isoenzymes has major implications for drug synthesis, biotransformation, and

disposal. Studies show that five major isoforms are substrates for 50% to 90% of medical medicines (CYP1A2, CYP3A4, CYP2D6, CYP2C19, and CYP2C9) (Kirchmair *et al.*, 2015). The previous study showed that other chemicals are P-glycoprotein substrates/inhibitors but NQ and oxolinic acid are neither substrates nor inhibitors. The BBB permeability, logBBB> 0.3, is considered to cross the BBB easily in the distribution (D) study (Han *et al.*, 2020).

Toxicity Studies:

Gusar Test:

Software like GUSAR and SwissADME made it easier to determine these drugs' acute toxicity and pharmacokinetic characteristics (Lagunin *et al.*, 2011; Daina *et al.*, 2017). The lethal dosage 50 (LD_{50}) values of the five compounds were investigated for acute toxicity on mouse/rat models administered by oral, intravenous (IV), intraperitoneal (IP), and subcutaneous (SC) routes, as well as toxicity with reference to different organs to evaluate for detrimental effects on organs and their systems (Table 5). The rat IV LD_{50} value of Apigenin, Xanthomicrol, Eriodictyol, Kaempferol and Luteolin was determined to be 229,700 mg/kg, 360,200 mg/kg, 1729,000 mg/kg, 392,600 mg/kg and 372,000 mg/kg, respectively. According to GHS the classes are, Class I: fatal if swallowed ($LD_{50} \leq 5$); class II: fatal if swallowed ($5 < LD_{50} \leq 50$); class III: toxic if swallowed ($50 < LD_{50} \leq 300$); class IV: harmful if swallowed ($300 < LD_{50} \leq 2000$); class V: may be harmful if swallowed ($2000 < LD_{50} \leq 5000$); and class VI: non-toxic ($LD_{50} > 5000$)(Ghosh *et al.*, 2019).

All the selected phytochemical compounds were predicted to be non-toxic in all routes of drug administration. Resveratrol, Arzanol, Genistein, Resveratrol, Ferulic Acid, Rosmanol and Thymohydroquinone have relatively low toxicity profiles and need high doses to produce toxic effects. While ferulic acid and resveratrol are Class 5 chemicals with little toxic effects, the remainder of the compounds are Class 4 chemicals with mild harmful effects (Mielke *et al.,* 2017). Fucoxanthin (FX) had a greater LD_{50} value than Siphonaxanthin (SX) when administered by IP, whereas SX had a higher LD_{50} value when administered through IV, oral, or SC routes. When taken via IP and oral routes, FX and SX are classified as Class 4 chemicals by the OECD, however they are Class 3 chemicals when administered using IV and SC routes (Yim *et al.,* 2021).When compared to the other studies, drug molecules in current study were found to be non-toxic in all routes of drug administration (rat model).

Environmental toxicity- ECOSAR Test:

The environmental toxicity was analyzed by using ECOSAR test which is represented in Table 6. Eriodictyol showed very less toxicity in fish (96 h), Daphnid (48 h) and green algae (96 h). In comparison to other compounds, Kaempferol showed more toxic effect on aquatic organism (Table 6). A total of 13 models were used for examining the environmental toxicity using Vega software. The results from the ECOSAR, EPA and T.E.S.T., models were quite similar (Jiménez-Holgado *et al.*, 2021). For fish, invertebrates, and algae, the measured acute impact concentrations vary from 388 mg/l to 4 mg/l, while the ECOSAR predicted acute effect values range from 89 mg/l to 25 mg/l. Whereas ECOSAR-predicted ChV (chronic toxicity value) range from a high of 9.6 mg/l to a low of 5.1 mg/l, measured chronic NOECs for Daphnia and green algae range from a high of 24 mg/l to a low of 0.5 mg/l (Weeks *et al.,* 2012). In comparison to previously studied compounds, the screened ligands in this study were determined to be less toxic (Eriodictyol-180.009 mg/l).

Toxicity analysis-ProTox test:

The ProTox-II website has unique prediction scheme that is divided into distinct degrees of toxicity, such as oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints (such as mutagenicity, cytotoxicity, and immunotoxicity), for analyzing adverse effects of drug molecule (Banerjee *et al.*, 2018). A chemical's toxicity can be assessed using several endpoints, including mutagenicity, and many more. Moreover, it can be

Table 5: Results of LD_{50} value of the compound estimated with Rat toxicity model

Ligands	Rat IP LD_{50} (mg/kg)	Rat IV LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	Rat SC LD_{50} (mg/kg)
Apigenin	689,100	229,700	896,600	5118,000
Xanthomicrol	785,100	360,200	1311,000	3320,000
Eriodictyol	1422,000	1729,000	1006,000	2123,000
Kaempferol	1163,000	392,600	2183,000	5938,000
Luteolin	1573,000	372,000	1684,000	2723,000

Table 6: Results of LD_{50} value of the compound estimated with ECOSAR Test

Ligands	ECOSAR TEST		
	Organism	Duration	mg/L (ppm)
Apigenin	Fish	96 h	38.718
	Daphnid	48 h	23.767
	Green Algae	96 h	24.439
Xanthomicrol	Fish	96 h	85.298
	Daphnid	48 h	51.096
	Green Algae	96 h	47.490
Eriodictyol	Fish	96 h	180.009
	Daphnid	48 h	103.469
	Green Algae	96 h	81.077
Kaempferol	Fish	96 h	9.436
	Daphnid	48 h	6.379
	Green Algae	96 h	9.778
Luteolin	Fish	96 h	110.702
	Daphnid	48 h	65.008
	Green Algae	96 h	55.650

quantified using LD_{50} (lethal dose) values and qualitatively using binary (active or inactive) measurements for certain cell types and assays or indication areas including cytotoxicity, immunotoxicity, and hepatotoxicity (Raies and Bajic, 2016). All the ligand molecules were inactive in case of immunotoxicity and hepatotoxicity (Table 7). Apigenin and Luteolin showed cytotoxic and mutagenic effects in ProTox test (Table 7). Anisotine was expected to be mutagenic and carcinogenic, and naringenin was predicted to be cytotoxic, they were rejected as drug molecules against SARS-CoV-2 (Mishra *et al.*, 2021). Scytonemin and its derivatives (SAR-CoV-2 Inhibitors) have been discovered to be carcinogenic, mutagenic, and cytotoxic, making them unsuitable therapeutic candidates (Sahu *et al*., 2022). There is no evidence that Rhamnocitrin, Isokaempferide and Kaempferol of *Artemisia annua* is hepatotoxic, carcinogenic, mutagenic, cytotoxic, or immunotoxic (Johnson *et al.*, 2022). FDA-approved medications like Glecaprevir,

Table 7: Toxicity panel – ProTox

Ligand	Hepatotoxicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Apigenin	Inactive	Inactive	Inactive	Active
Xanthomicrol	Inactive	Inactive	Inactive	Inactive
Eriodictyol	Inactive	Inactive	Inactive	Inactive
Kaempferol	Inactive	Inactive	Inactive	Inactive
Luteolin	Inactive	Inactive	Active	Inactive

Rilpivirine, and Dolutegravir are predicted to be immunotoxic in nature (Sepay *et al.*, 2021).

Molecular Docking:

The Molecular docking of screened compounds was docked against 6LU7, 7BTF and 1R4L using Auto dock vina and the results were summarized in the Tables 8-10. The first protein utilized for docking was PDB: 6LU7 SARS-CoV-2 M^{pro}, a potential target for the creation of a Covid-19 therapy. M^{pro} belongs to the protease protein family, which plays a key role in the development of many viruses. SARS-CoV-2 major protease catalytic site His41 and Cys145 are the two amino acids that make up M^{pro}. These two amino acids formed a catalytic duo that helps the virus mature (Chen, 2020; Mirza and Froeyen, 2020).

The second target was PDB: IR4L angiotensin-converting enzyme 2 (ACE2) and spike S1 domain protein interaction in the epithelial cells of the respiratory system, particularly the lungs controls this infection. Inhibiting ACE2 is a key strategy for managing Covid-19 (Koentjoro *et al.*, 2020). The inhibition of 7BTF (SARS-COV-2-RNA polymerase) has been proven to have a positive impact in Covid-19 treatment (Owona *et al.*, 2021). The binding energy, H-bond donor, H-acceptor and bond length interaction of drug molecules and protein targets are given in Tables 8-10. The binding energy of ligands Apigenin, Xanthomicrol, Eriodictyol, Kaempferol and Luteolin against the target 6LU7 was determined to be -7.8Kcal/mol, -6.9Kcal/mol, -7.7 Kcal/mol, -7.9 Kcal/mol and -7.1 Kcal/mol, respectively. Against the 6LU7, Kaempferol showed better binding energy of -7.9 Kcal/mol. Against the target 7BTF the ligands apigenin, Xanthomicrol, eriodictyol, Kaempferol and Luteolin showed the binding energy of -7.2 Kcal/mol, -6.1 Kcal/mol, -7.2 Kcal/mol, -7.0 Kcal/mol and -7.2 Kcal/mol, respectively. The binding energies of the ligands apigenin, Xanthomicrol, eriodictyol, Kaempferol, and Luteolin were determined to be -8.3Kcal/mol, -8.3Kcal/mol, -8.8Kcal/mol, -7.9 Kcal/mol, and -8.8 Kcal/mol against the target IR4L.

Among the five ligands, Eriodictyol showed better binding energy against the protein targets 6LU7, 7BTF and IR4L of SARS-COVID-19 indicating effective affinity. Indian red rice's Eriodictyol (-10.75 kcal/mol) has a higher binding affinity for the SARS-COV-2 M^{pro} than the control medication, Nelfinavir (-8.53 kcal/mol) (Rasaily *et al.*, 2021). Docking scores for 18 of the 31 phytoconstituents against Main Protease Spike protein and RNA dependent RNA polymerase of the virus are better than -6 kcal/mol. With Ashwagandhanolide, the best docking score of -9.9 kcal/mol was noted. Many more phytoconstituents, including Withaferin, Withacoagin, and Withanone, have docking scores that are close to -9 kcal/mol (Borse *et al.*, 2021). Sesami, Sesaminol, and Sesamolin, chemicals produced from *S. indicum*, docked with COVID-19 M^{pro} showed minimum binding affinities (-8.2, -7.8,- 7.7 kacl/mol) (Natesh *et al.*, 2021). The bioactives of *Emblica officinalis*, *Phyllanthus niruri* and *Tinospora cordifolia* may operate as potential COVID-19 M^{pro} inhibitors, according to earlier

Table 8: Binding energy and bond length of ligands interacting with 6LU7

S. No.	Ligands	6LU7			
		Binding energy (Kcal/mol)	H-donor	H-acceptor	Bond length(Å)
1	Apigenin	-7.8	Apigenin	Asp187A	3.452
			Apigenin	Leu141A	2.890
2	Xanthomicrol	-6.9	Xanthomicrol	Asp187A	2.952
3	Eriodictyol	-7.7	Eriodictyol	Leu141A	2.237
			Eriodictyol	Asp187A	2.885
4	Kaempferol	-7.9	Kaempferol	Asp188A	2.145
5	Luteolin	-7.1	Luteolin	Arg188A	2.657
			Luteolin	Thr190A	3.458
			Luteolin	Thr190A	3.250

Table 9: Binding energy and bond length of ligands interacting with 7BTF receptor

S. No.	Ligands	7BTF			
		Binding energy (Kcal/mol)	H-donor	H-acceptor	Bond length (Å)
1	Apigenin	-7.2	Ile68 C	Apigenin	2.986
2	Xanthomicrol	-6.1	Xanthomicrol	Gly427 A	5.226
3	Eriodictyol	-7.2	Asp711 A	Eriodictyol	3.178
4	Kaempferol	-7.0	Kaempferol	Asp36A	3.199
			Kaempferol	Leu49A	3.219
5	Luteolin	-7.2	Luteolin	Asp36A	2.764

Table 10: Binding energy and bond length of ligands interacting with IR4L

S. No.	Ligands	IR4L			
		Binding energy (Kcal/mol)	H-donor	H-acceptor	Bond length(Å)
1	Apigenin	-8.3	Apigenin	Pro346A	3.059
2	Xanthomicrol	-8.3	Xanthomicrol	Asp367 A	6.316
3	Eriodictyol	-8.8	Eriodictyol	Pro346 A	2.948
4	Kaempferol	-7.9	Kaempferol	Cys361A	3.181
5	Luteolin	-8.8	Luteolin	Pro34A	2.997

report (Murugesan *et al.,* 2021) and the findings of the current *in silco* investigation.

The complexities of SARS-CoV-2 have doomed the globe right now because to the lack of an effective drug. Nonetheless, several synthetic antiviral drugs such as lopinavir/ritonavir and remdesivir, as well as antimalarial drugs chloroquine and hydroxychloroquine, are available (Arabi *et al*., 2018; Bimonte *et al.*, 2020). The current treatments for SARS-CoV-2 patients

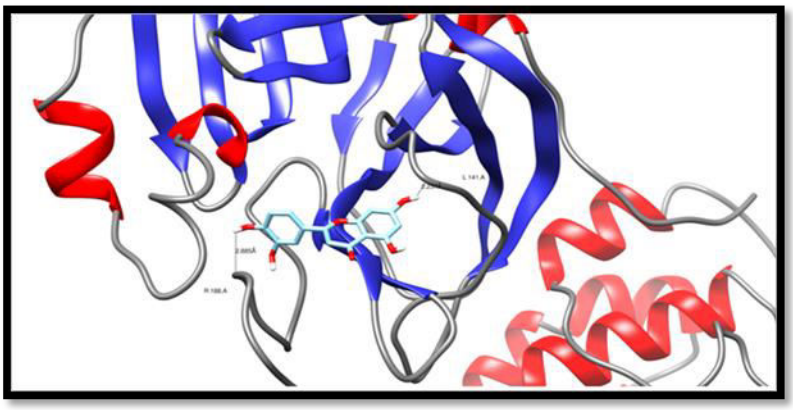

Fig. 2: Docking of Eriodictyol-6LU7 complex.

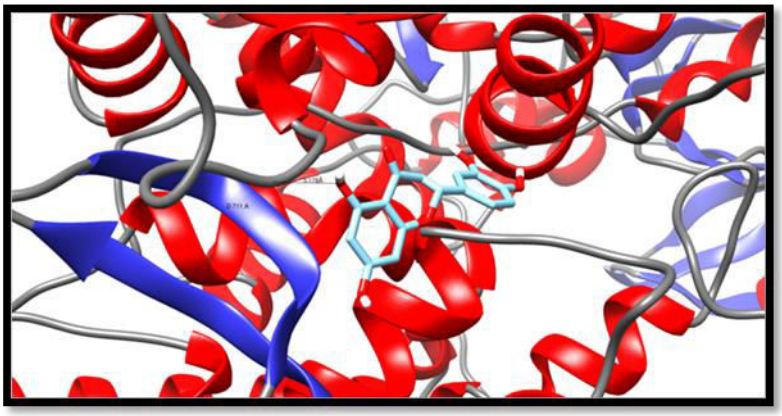

Fig. 3: Docking of Eriodictyol-7BTF complex.

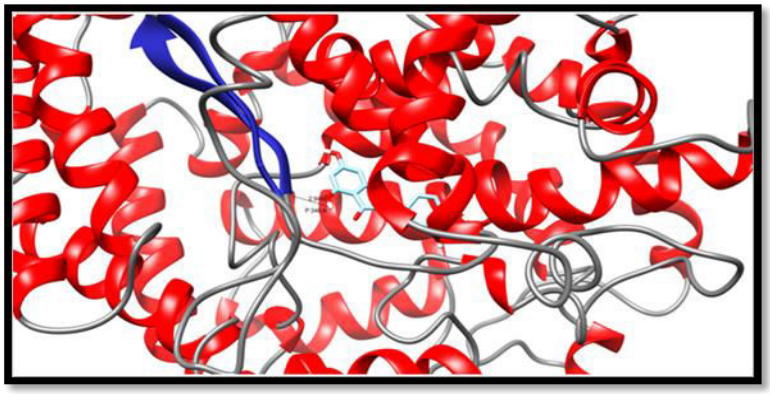

Fig. 4: Docking of Eriodictyol-IR4L complex.

have a variety of negative effects; hence natural drugs are desperately needed. Natural medicines can enhance immunity (Kyo *et al*., 2001). Many synthetic drugs fail in clinical trials due to poor ADMET properties. The orally available therapeutic medicine that target viral entrance and replication is the need of the hour. Many edible and therapeutic plants have been recommended as a therapeutic approach for infection prevention and treatment since their inception (Boukhatem and Setzer, 2020; Yang, 2020; Yang *et al*., 2021). Over-the-counter nutritional and dietary supplements may have anti-COVID-19 capabilities (Zabetakis *et al*., 2020;

Iddir *et al*., 2020; White *et al*., 2021).

In our study, Eriodictyol as a drug molecule against SAR-COV-2 target molecules showed good ADMET properties. The binding energy of Eriodictyol was better when compared to other drug molecules of *Ocimum basilicum*. Compared to previous studies, Eriodictyol (*Ocimum basilicum*) showed effective binding interaction with target molecules. These ACE-2 inhibitors are believed to inhibit ACE-2 by altering its structural composition or by affecting glycosylation, which prevents ACE-2 from arriving to the surface and blocking the virus's ability to enter the host cell (Gross *et al*., 2020). Hence, ACE-2 receptor could be an effective antiviral target. Norquinadoline A, deoxytryptoquivaline, and deoxynortrypto-quivaline, three naturally occurring alkaloids, exhibited substantial binding to the three targets, SARS-CoV-2 main protease, spike glycoprotein, and human angiotensin-converting enzyme 2. Therefore, additional research into these alkaloids as potential multi-target medications against COVID-19 has promise (Ismail *et al.*, 2021). The following drugs are recommended for the treatment of COVID- 1,2,3,4-tetrahydro-1-[(2-phenylcyclopropyl)sulfonyl]-trans-(8CI), Elvitegravir, Oxolinic acid and Rilapladib. These drugs are effective at targeting functional macromolecules of SARS-CoV-2 and have favourable ADMET properties (Alexpandi *et al.,* 2020). Eridictoyl with lowest binding energy against ACE-2 receptors can be a potent inhibitor. The molecular docking images of the drug molecule Eriodictyol with Covid-19 targets are given in Figures 2-4.

Conclusion

In recent period, the world's healthcare sector has been challenged by the spread of COVID-19. Virtual screening-based molecular docking was used to identify potential compounds with the ability to bind Covid 19 M^{pro}, SARS-CoV-2 RNA dependent RNA polymerase and Angiotensin Converting enzyme- Related carboxypeptidase. Our results demonstrated that Eriodictoyl in comparison with other ligands selected in current study showed better affinity towards SARS-CoV-2 targets. In particular, Eriodictoyl- ACE-2 receptor complex showed binding energy of -8.8 Kcal/mol confirming its ability to perform as an ACE-2 inhibitor in combating COVID-19. However, further pre-clinical and clinical studies should be conducted to confirm the efficacy of the drug compound.

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