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ORIGINAL ARTICLE

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Aiming COVID-19 SARS-cov-2 proteins by natural antiviral flavonoids through *in-silico* drug repurposing

Karumalaiyan Palanisamy[1], Pandiyarajan Sabarison[2,5], Velayutham Gurunathan[3], Govindasamy Hariharan[4], Ho-Chiao Chuang* [2], Sheng-Tung Huang[5]

[1] *Department of Chemistry, Srinivasan College of Arts and Science, Perambalur 621 212, Tamil Nadu, India.*

[2] *Department of Mechanical Engineering, National Taipei University of Technology, Taipei-10608, Taiwan.*

[3] *Postgraduate & Research Department of Chemistry, Bishop Heber College, Tiruchirappalli, Tamil Nadu, India.*

[4] *Research Associate, School of Sciences, Bharata Mata College (Autonomous), Thrikkakara-682021, Kochi, Kerala, India.*

[5] *Department of Chemical Engineering and Biotechnology, National Taipei University of Technology, Taipei-10608, Taiwan.*

*E-Mail: ***hchuang@mail.ntut.edu.tw***

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The World Health Organisation (WHO) has proclaimed the quickly spreading, extremely infectious, and pathogenic SARS-CoV-2 (SARS-Coronavirus 2) linked COVID-19 (Coronavirus disease 2019) a pandemic. SARS-CoV-2 conquers host cell by connecting glycoprotein (S-protein) spike viral surface with ACE2 (cellular angiotensin converting enzyme 2). That necessary virus molecular association through host cell provides clear beneficial goal on behalf of discovering SARS-CoV-2 antiviral medications. These medications recycling will offer fast and possible therapy to extend COVID-19 exponentially. The present study is to estimate and classify natural antiviral analogues as repurposing medicines like 4',5-Dihydroxy,3,3',7-trimethoxyflavone, 3,3'-Dimethoxyquercetin, Fisetin, O-Glucosyl-7-methyl-5-genistein, Glycosil-7-O-luteolin, Hesperetin, Isoquercitrin, Justicidin B, Luteolin–7-O-glucoside and Morin for COVID-19 main protease and compared with antiviral medication Remdesivir. Molecular docking studies have shown that Luteolin–7-O-glucoside and Justicidin B were natural flavonoid derivative of exceptional inhibition ability through binding energy of -9.5,-9.4 kcal/mol of 5N5O and 6LU7 enzyme, relative to the other compounds and Remdesivir antiviral medication (Binding energy -7.4 and -7.7 Kcal/mol). The need for the most time is the prompt discovery and commitment of appropriate medication to tackle and convince the global COVID-19 crisis. Besides, timely in vivo experiments were needed to approve the inhibition efficacy of the anti-SARS-CoV-2 compounds.

Key words: Anti-viral, ADME, COVID-19, Justicidin B, Luteolin–7-O-glucoside, Molecular docking

There is a horrific worldwide public health epidemic as a consequence of a febrile respiratory pandemic such as air syndrome triggered via latest coronavirus, dubbed SARS-CoV-2, which triggers COVID-19. The representative of the Coronaviridae group was SARS-CoV-2, that is an optimistic strategy-intellect, enclosed beached RNA virus that causes contagions of marine, mammalian, and avian organisms throughout the globe (Wan *et al*., 2020; Malik *et al*., 2020). Medical initiation of COVID-19 disease is described through fatigue, dry cough, multi-organ failure, fever, and sometimes mortality in extreme cases (Huang *et al*., 2020). As of April 13, 2020, over 1,800,000 people have been adversely affected worldwide, and over 100,000 deaths from Interior China and other 213 pretentious countries have already been reported (WHO, 2020). Alpha-coronavirus infections (NL63-CoV and HCoV-229E) are mostly asymptomatic and trivial, while beta-coronaviruses, together with MERS-CoV (Middle East Coronavirus Respiratory Syndrome) and SARS-CoV, have triggered severe diseases (Liu *et al*., 2020). In 2002, the SARS-CoV epidemic formed in China and contributed to 8,000 cases testified (WHO, 2015). Later in Saudi Arabia, recurrence in the form of MERSCoV was recorded at 35% of the fatality rate (WHO, 2016; Huang *et al*., 2020).

HCoV-HKU1, HCoV-OC43, and NL63-CoV have limited other human-infected coronaviruses (Gaunt *et al*., 2010). The coronaviral reappearance, by way of SARS-CoV-2 did by the finale of 2019, devours frightened the globe and developed a troubling state of affairs needing immediate care to avoid the prospective passing of contaminated patients (Malik *et al*., 2020; Smith & Freedman, 2020). Despite substantial clinical work globally, no appropriate antiviral medications or treatments to cure people or avoid the virus's spread are still used. Present measures to deter human-to-human infection are geared to quarantine and containment of diseased patients (Smith & Freedman, 2020; Wu & McGoogan, 2020). Therefore, reports are available on the repurpose of antiviral medicines such as anti-malarial, ritonavir, lopinavir, and remdesivir in contradiction of SARS-CoV-2 (Touret & Lamballerie, 2020). Also, monoclonal antibody neutralization therapies remain now produced to tackle the COVID-19 epidemic (Elshabrawy *et al*., 2012; Dhama *et al*., 2020). In human beings, coronavirus infection is guided primarily by associations amongst host cell receptor (ACE2) and the SProtein (envelope-anchored spike glycoprotein) of the coronavirus (Hoffmann *et al*., 2020; Wong *et al*., 2004). Environmental and economic characteristics can significantly promote the efflux of secondary metabolites such as tropical plant bioactive compounds. Additionally, secondary plant-concealed metabolites are deemed prodigiously in tropical regions and are progressed in remedies (Guerriero *et al*., 2018; Yang *et al*., 2018). Innumerable medicinal plant natural products were already evaluated for antiviral action (Zakaryan *et al*., 2017; Seema & Thyagarajan, 2016; Jo *et al*., 2020).

The natural flavonoid analogue **4',5-Dihydroxy,3,3',7-trimethoxyflavone** was extracted from the Chinese therapeutic plant, *Agastache rugosa* Kuntze (*Labiadae*) and displayed a potent antiviral effect against picornavirus (Ishituska *et al*., 1982). Natural flavonoid derivative methoxyflavone **3, 3'-Dimethoxyquercetin** was isolated from the medicinal plants *Veronia amygdalina* Del. (*Compositae*) and *Euphorbia grantii* Oliv. (*Euphorbiaceae*) exhibiting incredible antiviral activity against vesicular stomatitis virus and picornaviruses (Hoff *et al*., 1989; Rwangabo *et al*., 1986). The natural flavonoid derivative **Fisetin** displayed a significant antiviral effect against pseudorabies virus and extracted from the medicinal plant *Rhus* spp. (*Anacardiaceae*) (Beladi *et al*., 1977). Natural flavonoid analogue ***O*-Glucosyl-7-methyl-5-genistein** showed significant antiviral effect against herpes virus and extracted from the therapeutic plant *Ulex europaeus* L. (*Leguminosae*) (Swallow *et al*., 1975). An antiviral natural flavonoid derivative **Glycosil-7-*O*-luteolin** was isolated from the methanolic extract of *Matricaria inodora* L. (*Compositae*) and displayed remarkable antiviral activity against poliomyelitis and herpes viruses. The natural flavonoid analogue **Hesperetin** predominantly present in sweet oranges and lemons; showed significant antiviral effect besides vesicular stomatitis virus and extracted from the

medicinal plant *Citrus* spp. (*Rutaceae*) (Harborne, 1988). The natural antiviral flavonoid derivative **Isoquercitrin** revealed significant effect in contradiction of Herpes simplex type 1 virus and extracted from the medicinal plant *Waldsteinia fragarioides* Michx. (*Rosaceae*) (Karam & Shier, 1992). Antiviral natural flavonoid analogue **Justicidin B** displayed remarkable antiviral effect against Sindbis virus, murine, and cytomegalovirus and isolated from the medicinal plant *Phyllanthus acuminatus* (*Euphorbiaceae*). The natural flavone derivative, **Luteolin–7-*O*-glucoside**, showed significant antiviral effect against poliovirus and herpes virus and extracted from the medicinal plant *Matricaria inodora* L. (*Compositae*) (Beladi *et al*., 1977). An antiviral flavones analogue, **Morin** displayed remarkable antiviral activity against pseudorabies virus and extracted from the therapeutic plant *Chlorophora tinctoria* L. Gaud (*Moraceae*) (Beladi *et al*., 1977). Figure 1 represents the natural antiviral analogues. We also looked at **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**, **Luteolin–7-*O*-glucoside** and **Morin** as possible SARS inhibitor candidates (PDB ID: 5N5O and 6LU7), as well as **Nelfinavir**, an antiviral medication. The findings of this report will give more researchers the prospect of discovering the correct COVID-19 medicines.

MATERIALS AND METHODS

In-silico docking

In-silico assessments were being used for binding mode examination, an association of phytoconstituents **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**, **Luteolin–7-*O*-glucoside**, **Morin** and anti-viral **Remdesivir** with SARS coronavirus proteins (PDB ID: 5N5O and 6LU7) by Autodock vina 1.1.2 (Trott & Olson, 2010). Protein Data Bank (http:/www.rcsb.org) has been employed to obtain the SARS coronavirus main proteases (PDB ID: 5N5O) and (PDB ID: 6LU7) crystal structures. Chem3D Pro 12.0 and ChemDraw Ultra 12.0 programs were utilized to sketch the inhibitors' structures and energy minimization. The AutoDock Software 1.5.6 application bundle was used to build Autodock Vina input data. Discovery studio 2019 program package was utilized for binding pocket prediction of main protease (PDB ID: 5N5O and 6LU7) via co-crystallized ligands. The 5N5O Protein Quest Grid has been recognized as centre x,y,z: -23.002, -3.023, 4.681 with measurements x,y,z: 24 through 1.0 Å interval. The 6LU7 protein quest grid was defined as centre x,y,z:-10.656, 17.223, 67.024 in dimension x,y,z: 20 in 1.0 Å positioning and meaning of completeness remained fixed to 8. The other restrictions have been fixed and not specified by default for Autodock Vina. The compound which devotes the smallest inhibitory value is the main inhibitor, and the consequences were visually examined by Discovery studio 2019.

Molecular property and ADME prediction

Herein, Lipinski's law of five' being utilized for the theoretical prediction of ADMEs and the toxicity of **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**, **Luteolin–7-*O*-glucoside**, **Morin** and antiviral **Remdesivir** compounds (Lipinski *et al*., 2001). A Swiss ADME online tool was also used to estimate the Lipinski parameters (Swiss ADME, 2020). To predict the transportation and biocompatibility of an active compound over blood-brain obstacle, the tPSA (topological polar surface) has been utilized (Ertl *et al*., 2000). Bioavailability is too multidimensional but mainly concerned with the absorption of the digestive system (Daina & Zoete, 2016). The percentage of absorption remained determined as of formulas: percent ABS = 109 (TPSA x 0.345). Further predictions involved CYP2D6, PLD (phospholipidosis), P-glycoprotein inhibition, water solubility, and CYP2D9.

RESULTS AND DISCUSSION

In-silico assessment

In-silico docking replications remained carried out to progress appreciative of the conceivable progression of biotic activity. Phytoconstituents **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**,

Luteolin–7-*O*-glucoside and **Morin** as well as antiviral **Remdesivir** compounds were evaluated for their inhibition capability concerning SARS coronavirus proteins 5N5O and 6LU7 through the software Autodock Vina. All these checked inhibitors demonstrate negative binding energy. The natural derivative **Luteolin–7-*O*-glucoside** demonstrates astonishing inhibition capability through binding ability of -9.5 kcal/mol over former derivatives **4',5-Dihydroxy,3,3',7-trimethoxyflavone** (-7.4kcal/mol), **3,3'-Dimethoxyquercetin** (-7.3 kcal/mol), **Fisetin** (-7.3 kcal/mol), ***O*-Glucosyl-7-methyl-5-genistein** (-7.7 kcal/mol), **Glycosil-7-*O*-luteolin** (-8.1 kcal/mol), **Hesperetin** (-7.4 kcal/mol), **Isoquercitrin** (-7.4 kcal/mol), **Justicidin B** (-7.8 kcal/mol), **Morin** (-7.5 kcal/mol) and antiviral drug **Remdesivir** (-7.4 kcal/mol) in 5N5O receptor individually. The essential aspect of bonding equilibrium between ligand and proteinis hydrogen bonding, and the supporting bonding gap between atoms H-acceptor and H-donor is less than 3.5 Å (Taha *et al*., 2015). The related hydrogen bonding distances for the specific object receptor inhibitors remained fewer than 3.5 Å, demonstrating the strong hydrogen link amongst ligands and receptors. **Luteolin–7-*O*-glucoside** demonstrates two associations between hydrogen bonding and the 5N5O receptor. Asn142 and Gly143 amino acid residues were associated with bond lengths of 3.09 and 2.12 Å in contact with hydrogen. The residues of Met49, Cys145, and Gln189 amino acids came in contact with hydrophobics. Figure 2 indicates the hydrophobic and hydrogen bonding interaction of compound **Luteolin–7-*O*-glucoside** with amino acid residues in 5N5O protein. The antiviral **Remdesivir** treatment demonstrates two associations with hydrogen bonding with the target 5N5O. Cys44 and Glu166 amino acid residues are entangled through associations between hydrogen and the bond lengths 2.20 and 2.49 Å. Thr25, Met165, Leu167, Pro168, and Gln189 amino acid residues were mixed within hydrophobic encounters. Figure 3 indicates the hydrophobic and hydrogen bonding interaction of **Remdesivir** antiviral medication with amino acid residues in 5N5O receptor.

Table 1 displays the molecular interactions of natural analogues on target protein 5N5O. **Justicidin B** natural flavonoid analogue demonstrates impressive inhibition capacity through binding ability of -9.4 kcal/mol relative to other derivatives **4',5-Dihydroxy,3,3',7-trimethoxyflavone** (-7.2 kcal/mol), **3,3'-Dimethoxyquercetin** (-7.2 kcal/mol), **Fisetin** (-7.3 kcal/mol), ***O*-Glucosyl-7-methyl-5-genistein** (-7.9 kcal/mol), **Glycosil-7-*O*-luteolin** (-7.8 kcal/mol), **Hesperetin** (-7.1 kcal/mol), **Isoquercitrin** (-7.8 kcal/mol), **Luteolin–7-*O*-glucoside** (-7.9 kcal/mol), **Morin** (-8.4 kcal/mol) and antiviral drug **Remdesivir** (-7.7 kcal/mol) in 6LU7 protein individually. Compound **Justicidin B** displays one H-bonding contacts through receptor 6LU7. Gly143 amino acid residue was entangled into correlations between hydrogen and the bond lengths of 1.89 Å. The amino acid residues Met49, Phe140, and Cys145, have been entangled in hydrophobic encounters. Figure 4 demonstrated the bonding of hydrogen and hydrophobic constructions of amino acid residues with the **Justicidin B** compound in the 6LU7 protein. The antiviral medication **Remdesivir** demonstrates six associations between hydrogen and receptor 6LU7. The residues of Thr26, Cys44,Gly143, Cys145, and Glu166 amino acids were entangled in hydrogen bonding to the 2.08, 2.87, 2.16 & 2.73, 3.00, and 2.38 Å bonding ranges. The residues of the His41, Met49, and Met165 amino acids were in touch with hydrophobia. The hydrogen bonding and hydrophobic connexions with Remdesivir are seen in Figure 5 of amino acid residues in the 6LU7 protein. The findings revealed that **Luteolin–7-*O*-glucoside** and **Justicidin B** had exceptional inhibition capacity in their respective target proteins 5N5O and 6LU7 relative to other compounds. The findings of natural antiviral analogues against SARS coronavirus (PDB ID: 6LU7) have been shortened in Table 2.

Molecular property and ADME prediction

The growth of bioactive components as healers is driven by high oral bioavailability (Newby *et al*., 2015). This analysis's key forecasters were demonstrated, for example, the intestinal absorption, low polar surface region, decreased molecular versatility, and hydrogen bonding ability (Azam *et al*., 2012). The natural antiviral analogues **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Hesperetin**, **Isoquercitrin**,

Justicidin B, and **Morin** satisfies Lipinski's "law of 5" without any infringement and compounds **Glycosil-7-*O*-luteolin**, **Luteolin–7-*O*-glucoside** and **Remdesivir** Fails "Rule of 5" with two infringement HBA, MW > 500, HBD and RoB (Table 3).

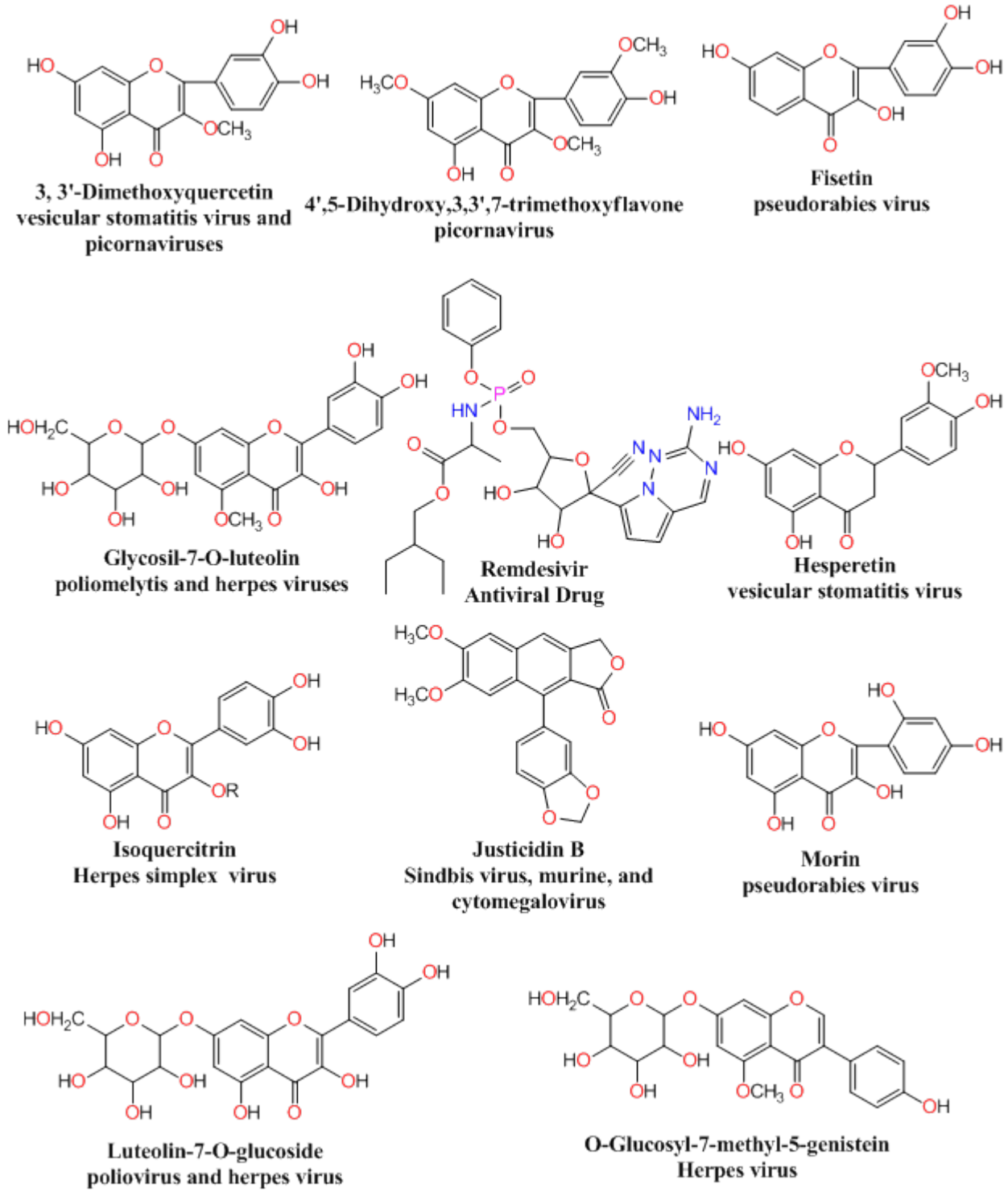

Figure 1: Natural antiviral derivatives.

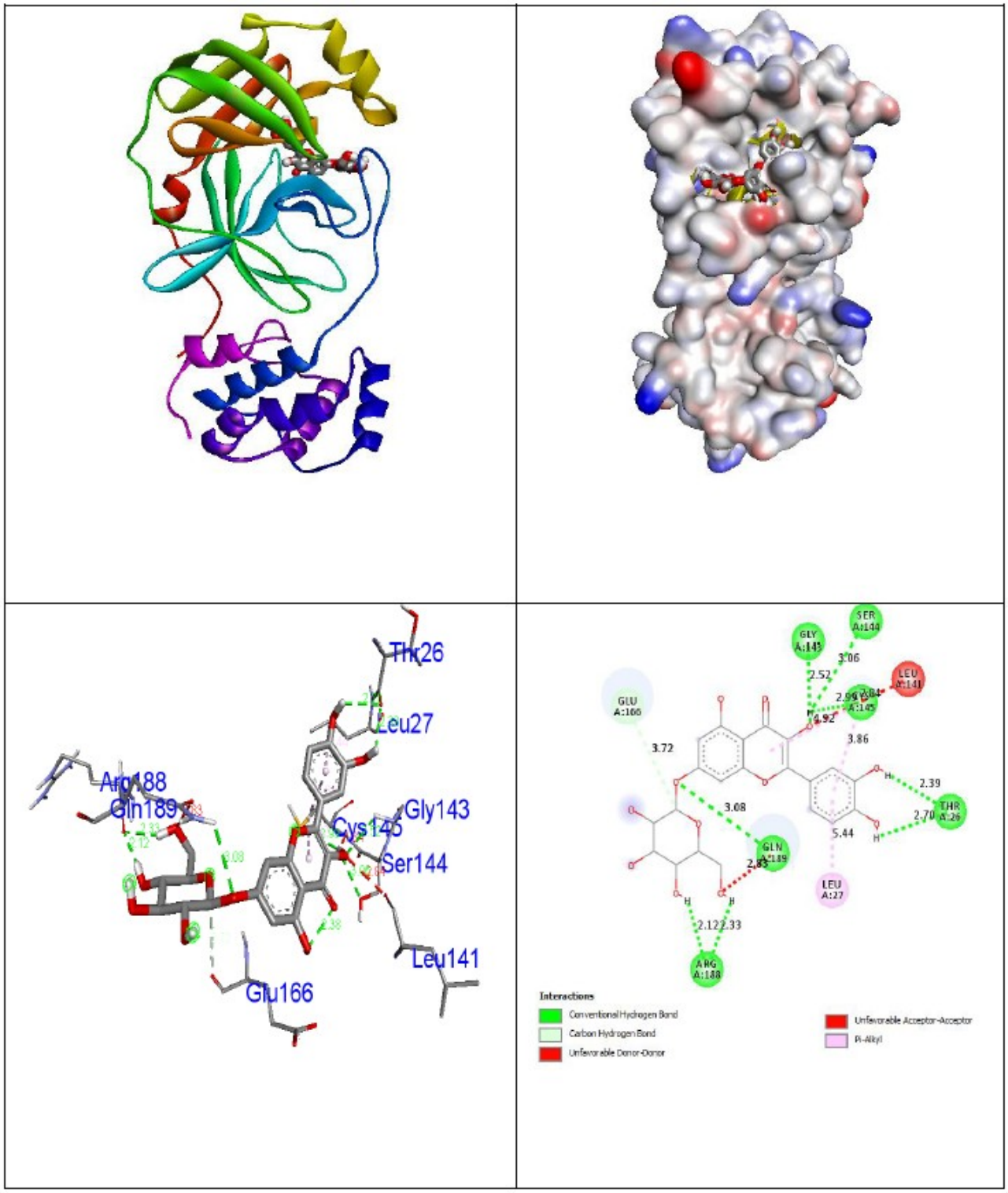

Figure 2: Interactions of **Luteolin–7-*O*-glucoside** inside the binding pocket of receptor **5N5O**.

Figure 3: Interactions of antiviral drug **Remdesivir** inside the binding pocket of receptor **5N5O**.

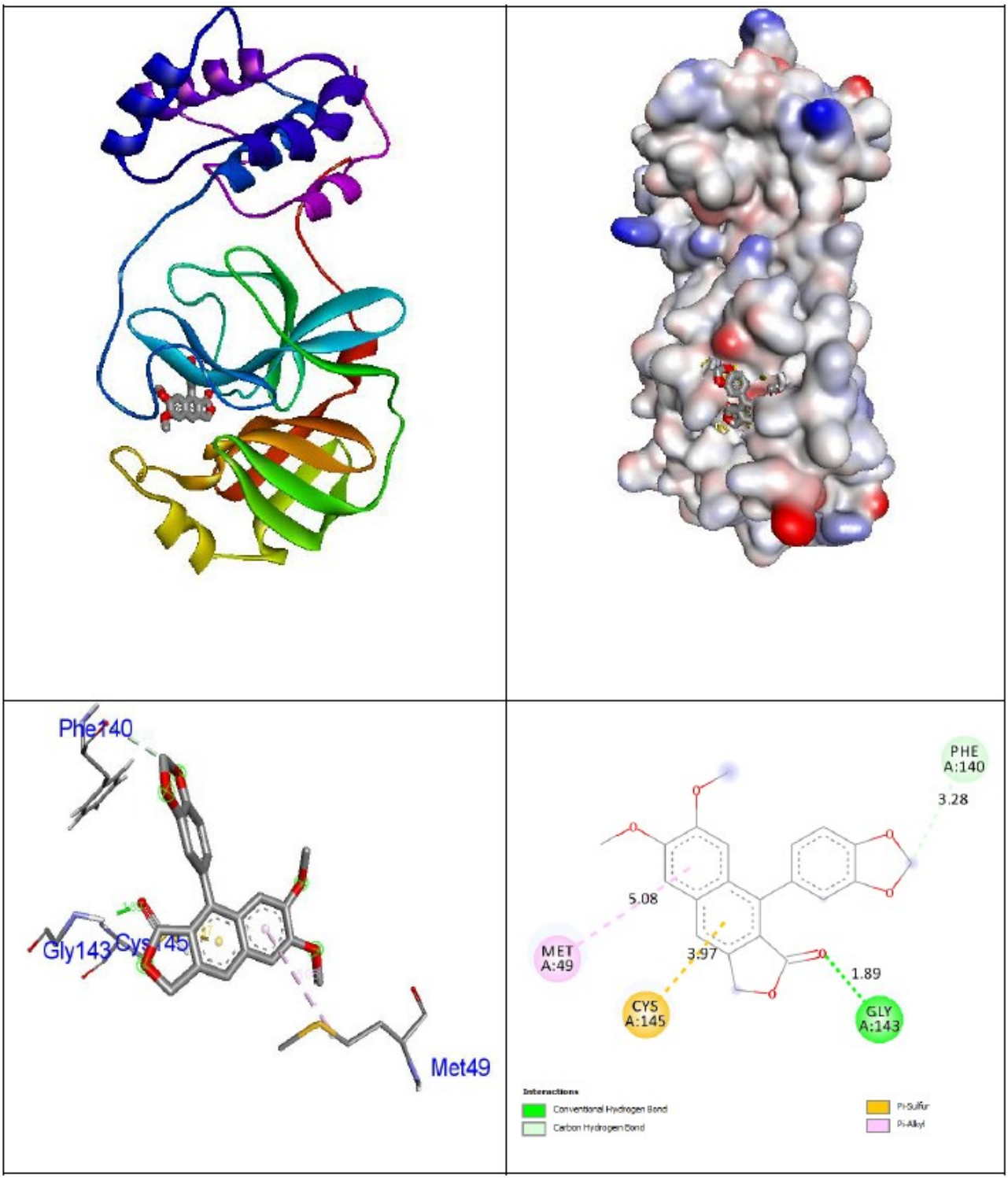

Figure 4: Interactions of **Justicidin B** within the binding pocket of receptor **6LU7**.

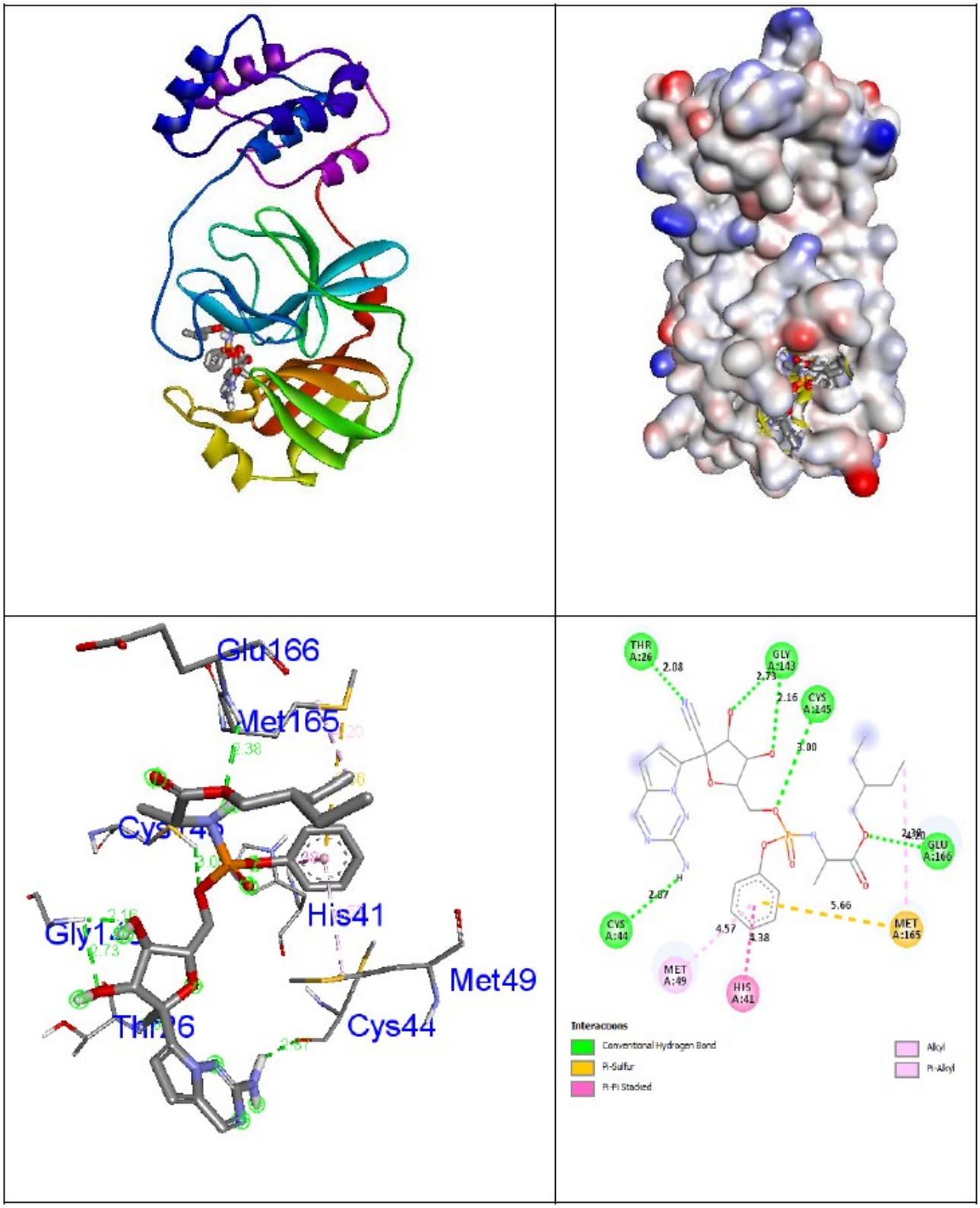

Figure 5: Interactions of antiviral drug **Remdesivir** inside the binding pocket of receptor **6LU7**.

Table 1. Interactions of compounds (**1a-1k**) against SARS coronavirus key protease (PDB ID: 5N5O).

Compounds	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
4',5-Dihydroxy,3,3',7-trimethoxyflavone (1a)	-7.4	2	Gly143, Cys145
3,3'-Dimethoxyquercetin (1b)	-7.3	1	Gly143
Fisetin (1c)	-7.3	1	Glu166
***O*-Glucosyl-7-methyl-5-genistein (1d)**	-7.7	6	Thr26, Gly143, Glu166, Arg188. Gln189
Glycosil-7-*O*-luteolin (1e)	-8.1	3	Thr26, Gln189, Thr190
Hesperetin (1f)	-7.4	3	Asn142, Glu166, Arg188
Isoquercitrin (1g)	-7.4	3	Gly143, Ser144
Justicidin B (1h)	-7.8	2	Gly143, Cys145
Luteolin–7-*O*-glucoside(1i)	-9.5	8	Thr26, Gly143, Ser144, Cys145, Arg188, Gln189
Morin (1j)	-7.5	1	Arg188
Remdesivir (1k)	-7.4	2	Cys44, Glu166

Table 2. Interaction of compounds (**1a-1k**) against SARS coronavirus key protease (PDB ID: 6LU7).

Compounds	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
4',5-Dihydroxy,3,3',7-trimethoxyflavone (1a)	-7.2	1	Gly143
3,3'-Dimethoxyquercetin (1b)	-7.2	0	-
Fisetin (1c)	-7.3	0	-
***O*-Glucosyl-7-methyl-5-genistein (1d)**	-7.9	6	Phe140, Asn142, Cys145, Glu166, Asp187
Glycosil-7-*O*-luteolin (1e)	-7.8	5	Thr24, Ser144, Cys145, Glu166, Arg188
Hesperetin (1f)	-7.1	3	Leu141, Arg188, Thr190
Isoquercitrin (1g)	-7.8	2	Leu141, Ser144
Justicidin B (1h)	-9.4	1	Gly143
Luteolin–7-*O*-glucoside(1i)	-7.9	5	Thr26, Cys44, Ser144, Cys145
Morin (1j)	-8.4	3	Gly143, Ser166, Asp187
Remdesivir (1k)	-7.7	6	Thr26, Cys44, Gly143, Cys145, Glu166

Table 3 Molecular property and computer-generated ADME (absorption, distribution, metabolism, excretion) forecast of potent compounds (**1a-1k**).

Compound	tPSA[a]	%Abs[b]	MW[c]	RoB[d]	HBD[e]	HBA[f]	MR[g]	IlogP[h] (MlogP)	LogS[i]	CYP2D6 Inhibitor
Rule	≤140 ´Å^2	**>50**	≤500	≤10	≤5	≤10	40–130	<5	>-4	**-**
4',5-Dihydroxy,3,3',7-trimethoxyflavone (1a)	98.36	75.06	344.32	4	2	7	91.44	3.26 (0.17)	-4.46	Yes
3,3'-Dimethoxy quercetin (1b)	120.36	67.47	316.26	2	4	7	82.50	2.00 (-0.31)	-3.89	Yes
Fisetin (1c)	111.13	70.66	286.24	1	4	6	76.01	1.50 (-0.03)	-3.35	Yes
***O*-Glucosyl-7-methyl-5-genistein (1d)**	159.05	54.12	446.40	5	5	10	110.58	1.93 (-1.39)	-3.05	No
Glycosil-7-*O*-luteolin (1e)	199.51	40.16	478.40	5	7	12	114.63	1.50 (-2.37)	-2.91	No
Hesperetin (1f)	96.22	75.80	302.28	2	3	6	78.06	2.25 (0.41)	-3.62	No
Isoquercitrin (1g)	131.36	63.68	302.24	1	5	7	78.03	1.63 (-0.56)	-3.16	Yes
Justicidin B (1h)	63.22	87.18	364.35	3	0	6	97.76	3.15 (2.60)	-4.85	Yes
Luteolin–7-*O*-glucoside(1i)	210.51	36.37	464.38	4	8	12	110.16	1.54 (-2.59)	-3.04	No
Morin (1j)	131.36	63.68	302.24	1	5	7	78.04	1.47 (-0.56)	-3.16	Yes
Remdesivir (1k)	213.36	35.39	602.58	14	4	12	150.43	2.74 (0.18)	-4.12	No

Abbreviations: [a] Topological polar surface area; [b] Absorption; [c] Molecular weight; [d] Number of rotatable bonds; [e] Number of hydrogen bond donors; [f] Number of hydrogen bonds acceptors; [g] Molar refractivity; [h] Logarithm of compound partition coefficient between n-octanol and water; [i] Logarithm of water solubility.

The molecular conformational changes defined the number of revolving ties and the potential for the receptor binding. Phytoconstituents **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**, **Morin**, **Glycosil-7-*O*-luteolin**, **Luteolin–7-*O*-glucoside** were under ten rotatable bonds except for **Remdesivir** (14 rotatable bonds), which are formed without the chirality core and have poor oral bioavailability conditions. The belongings tPSA (topological Polar Surface Area) reveals passive molecular transport across membranes and blood-brain barrier penetration (Ertl *et al*., 2000).

Checked substances except for compounds ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Luteolin–7-*O*-glucoside**, and **Remdesivir** with tPSA values < 140Å^2 fulfill the requirements for subsequent oral administration for gastrointestinal absorption. In comparison, all of the compounds studied except for ***O*-Glucosyl-7-methyl-5-genistein** (tPSA = 159.05Å^2**),** **Glycosil-7-*O*-luteolin** (tPSA = 199.51 Å^2), **Luteolin–7-*O*-glucoside** (tPSA = 210.51 Å^2), **Morin** (tPSA = 131.36

Å^2), **Isoquercitrin** (tPSA = 131.36 Å^2), **Fisetin** (tPSA = 111.13 Å^2), **Hesperetin** (tPSA = 96.22 Å^2), **4',5-Dihydroxy,3,3',7-trimethoxyflavone** (tPSA = 98.36 Å^2), **3,3'-Dimethoxyquercetin** (tPSA = 120.36 Å^2), and **Remdesivir** (tPSA = 213.36 Å^2) devour lower blood-brain barrier (tPSA > 90 Å^2), which reveals detrimental belongings of CNS (Central Nervous System).

The tested compounds except **Glycosil-7-*O*-luteolin** (% Abs = 40.16) and **Luteolin–7-*O*-glucoside** (% Abs = 36.37) demonstrated absorption percentage (percentage Abs = > 50), suggesting strong bioavailability. Bioavailability by oral route was appropriate (> 50 percent). The compounds **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Luteolin–7-*O*-glucoside** and **Morin** were very water-soluble (-logS > -4) excluding than other derivatives **4',5-Dihydroxy,3,3',7-trimethoxyflavone** (-logS-4.46), **Justicidin B** (-logS -4.85) and **Remdesivir** (-logS -4.12) have modest water solubility. Liver impairment side effects remained not suspected in the case of derivatives ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Luteolin–7-*O*-glucoside**, and **Remdesivir** since they were predicted to be CYP2D6 non-inhibitors. A part of the P-gp (P-glycoprotein) family transporter ABC (ATP-binding cassette) comprises the pharmaceutical metabolism, intestinal absorption, and brain penetration; its caginess may expressively modify the bioavailability and defense of the drug (Fromm, 2000). Phospholipidosis convinced medication is a condition known for further developing phospholipids in soft tissue and medication-associated poisonousness (Nonoyama & Fukuda, 2008).

The findings indicate that the studied natural derivatives **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, **3,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**,**Glycosil-7-*O*-luteolin**, **Isoquercitrin**, **Luteolin–7-*O*-glucoside**, and **Morin** were not a part of the P-gp substrate, and phospholipidosis was not promoted. The checks for P-gp-phospholipidosis were anticipated in **Hesperetin**, **Justicidin B**, and **Remdesivir**. The overall findings of ADME and toxicity indicate respectable pharmacological profile and rapid gastrointestinal ingestion through blood-brain blood barrier penetration in the isolated compound was **Justicidin B**. All assessed compounds remained acknowledged by way of drug-like and passed "Rule of 5" of Lipinski except **Glycosil-7-*O*-luteolin**, **Luteolin–7-*O*-glucoside**, and **Remdesivir**. The restrictions predicted are all within the context of accepted principles.

CONCLUSIONS

COVID-19 devours arisen in the anthropological community in China and is a possible danger to well-being internationally. However, here is no precisely approved medication to overcome the situation. The already offered COVID-19 medications coping with essential protease. The present work aimed to inspect some natural analogues extracted from medicinal plants that might be tossed off to combat COVID-19. The utmost frequently proposed phytoconstituents in healing plants that may function by way of substantial inhibitors of COVID-19 essential proteases (PDB ID: 5N5O, 6LU7) were **4',5-Dihydroxy,3,3',7-trimethoxyflavone**, 3**,3'-Dimethoxyquercetin**, **Fisetin**, ***O*-Glucosyl-7-methyl-5-genistein**, **Glycosil-7-*O*-luteolin**, **Hesperetin**, **Isoquercitrin**, **Justicidin B**, **Luteolin–7-*O*-glucoside** and **Morin** with negative binding energies. Studies in molecular docking have shown that compounds **Luteolin–7-*O*-glucoside** and **Justicidin B** were natural flavonoid derivative of exceptional inhibition ability through binding energy of -9.5, -9.4 kcal/mol of 5N5O and 6LU7 enzyme, relative to the other compounds and **Remdesivir** antiviral medication (Binding energy -7.4 and -7.7 Kcal/mol). However, an advanced study is necessary to inspect the possible application of these compounds in medicinal plants.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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