

Natural antiviral flavonoids: Striking successful repurposing against COVID-19 through in-silico docking

Velayutham Gurunathan¹, Chidambaram Sathishkumar²,
Hariharan Govindasamy^{3*}, Karumalaiyan Palanisamy⁴,
Periyanayagam Arockia Doss⁵

¹ Research Department of Chemistry, Bishop Heber College (Autonomous), (Affiliated to Bharathidasan University), Tiruchirappalli-620017, Tamil Nadu, India.

² Nextgen Academic Research, Perambalur-621107, Tamil Nadu- India.

³ Research Associate, School of Sciences, Bharata Mata College (Autonomous), Thrikkakara-682021, Kochi, Kerala, India.

⁴ Research Department of Chemistry, School of Science and Humanities, Dhanalakshmi Srinivasan University, Perambalur-621 212, Tamil Nadu, India.

⁵ Department of Chemistry, St. Joseph's College (Autonomous), Tiruchirappalli 620002, Tamil Nadu, India.

*E-Mail: haribiochemistry@gmail.com

Received February 23, 2025

Repurpose of recognized compounds and medications as anti-COVID 2019 (anti-CoVID-19) agents, in anti-SARS-CoV-2 operation, via biological re-assessment of their activities, is a recent and durable development for pandemic COVID-19 novel drugs in 2020. Even so, nearly all of the recorded inhibitors of the various phases of SARS-CoV-2 progression lacks severe forces towards main fateful SARS-CoV-2 enzymes (like the papain protease "PLpro", main protease "Mpro", and RNA-based RNA polymerase "RdRp"). The main objective of this article is to estimate and classify natural antiviral flavonoids as inhibitor medicines like Quercetin, Quercetagenin, Volkensiflavone, Ternatin, Meliternatin, Formononetin, Afromosin, Chrysosplenol B, Chrysosplenol C and Axillarin for COVID-19 main protease and compared with antiviral medication Remdesivir. *In-silico* docking studies devours natural flavonoid derivative Volkensiflavone was of exceptional inhibition ability (Binding energy-8.9, -9.0 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 takes place to approve inhibition efficacy of anti-SARS-CoV-2 compounds might save people are warranted.

Key words: Antiviral, ADME, COVID-19, Remdesivir, Volkensiflavone, Molecular docking

The COVID-19 global epidemic has driven the planet to pursue possible therapies to fight these destructive infectious diseases. According to the study, drugs produced by repurposing current medications are focussed on the destruction of virus pathogenicity (Manisha *et al.*, 2020). A modern coronavirus (2019-nCoV), generally alluded to as SARS-CoV-2 (severe acute respiratory syndrome Coronavirus 2), later appeared in Wuhan City in December 2019 (Hui *et al.*, 2020). Coronavirus is a non-segmented, enveloped virus of the *Coronaviridae* family, which has positive senses of genomic RNA. This specific epidemic is suspected to be linked to a crowded maritime sector in Wuhan, China, and closed since 23 January 2020 (Rupal *et al.*, 2020). The virus infects by overall 10,896,029 cases reported and 521,862 fatalities by 3 July 2020 and dispersed to 188 countries as per the CoVID-19 Console from the Johns Hopkins University Centre for Systems Science and Engineering (JHU) (Abo-Zeid *et al.*, 2020).

The dissemination of this enigmatic bread-packed virus, prompting highly effective control steps, continues to propagate to the human respiratory system (i.e. detected by a characteristic pulmonary infection) the virus-characteristic illness, coronavirus illness (COVID-19) in 2019 (i.e., key signs and symptoms localized and located). The epidemic of China's 2019 nCoV virus (starting with the Wuhan epidemic) takes feast through our world and devises world-wide epidemic of devastation and catastrophic catastrophe (Hui *et al.*, 2020; Li *et al.*, 2020). Since then, the intense besides finest exertions of global pharmacological firms, medication development testing centres/organizations, foreign health agencies, pharmaceutical/medical colleges and other relevant organizations have concentrated on prompt quest on behalf of successful effective drugs and rehabilitations capable of killing SARS-CoV-2, repetition of SARS-CoV-2, and combating the utmost stark and lethal possessions of COVID-19. No new antiviral drugs were formally and globally licensed so far in mid-2020 (Jiang *et al.*, 2020) for effective management of COVID-19.

Given the present non-appearance of proven successful anti-SARS-CoV-2 treatments and unadorned circumstance under the evolving global condition, several investigators have proposed the usage of some established active, potent drugs (Dong *et al.*, 2020), for instance, arbidol (anti-influenza) (Wang *et al.*, 2020), remdesivir (antiviral) (Choy *et al.*, 2020; Elfiky *et al.*, 2020; Elfiky *et al.*, 2020a; Shannon *et al.*, 2020; Wang *et al.*, 2020; Yin *et al.*, 2020), hydroxychloroquine (anti-malarial and anti-rheumatic disorientation) (Derwand *et al.*, 2020; Liu *et al.*, 2020), favipiravir (anti-influenza) (Cai *et al.*, 2020; Du *et al.*, 2020; Shiraki *et al.*, 2020), and ivermectin (anti-parasite) (Caly *et al.*, 2020), towards combat the original COVID-19. The prospects of several therapeutic and pharmacological chemists uses *in-silico* based molecular modelling studies to provide foundation for the production of innovative persuasive compounds active beside SARS-CoV-2, utmost of that placid in recently reported literatures (Amin *et al.*, 2020; Goyal & Goyal, 2020).

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; Thayil & Thyagarajan, 2016; Jo *et al.*, 2020). The natural flavonoid analogue **Quercetin** was extracted from the medicinal plant *Chenopodium quinoa* (Quenopodiaceae) and displayed remarkable antiviral activity against potato virus X (PVX) with 80% inhibition at <1µg/ml-1 (French *et al.*, 1992). Antiviral flavonoid **Quercetagetin** showed significant antiviral effect against several retroviruses comprising HIV and Rauscher murine leukaemia (RLV), along with cellular DNA polymerases and isolated from the many spp of *Compositae* flowers (Cody *et al.*, 1986). The natural antiviral flavonoid analogue **Volkensiflavone** displayed remarkable antiviral activity against influenza B virus and isolated from the therapeutic plant *Rhus succedania* L. (*Anacardaceae*) (Beladi *et al.*, 1977; Lin *et al.*, 1997). Natural antiviral 3-methoxyflavone derivative **Ternatin**

and **Meliteratin** showed significant antiviral effect against several viral pathogens including VSV type 2, HSV-1, poliovirus type 2, HSV-2, and adenovirus type 2; extracted from medicinal plant *Evodia madagascariensis* Baker (Rutaceae) (Simoes et al., 1990). Natural isoflavonoids **Formononetin** and **Afromosin** were displayed significant antiviral inhibitory effect against Epstein-Barr virus and obtained from the therapeutic plant *Wisteria brachybotrys* Sieb (Leguminosae) (Konoshima et al., 1989). Natural antiviral flavonoid analogues **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin**, were exhibited remarkable antiviral effect against rhinovirus and isolated from the medicinal plant *Chrysosplenium tosaense* (Saxifragaceae) (Tsuchiya et al., 1985). **Fig. 1** represents the natural antiviral analogues. This overall prevailing theme in the quest for vital compounds with structural stability to repurpose effectively as potential replacement drugs targeting COVID-19 directed us to screen natural antiviral flavonoids **Quercetin**, **Quercetagenin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin** as possible SARS inhibitor candidates (PDB ID: 5N5O and 6LU7), as well as **Remdesivir**, 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

Molecular docking tests were being used for binding mode examination, an association of compounds **Quercetin**, **Quercetagenin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C**, **Axillarin** and antiviral **Remdesivir** with SARS coronavirus proteins (PDB ID: 5N5O and 6LU7) by Autodock vina 1.1.2 (Trott et al., 2010). Protein Data Bank (<http://www.rcsb.org>) has been employed to obtain 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 structures of the inhibitors and too 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. 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 interval. The meaning of completeness were 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

Here in, Lipinski's 'Rule of five' being utilized for the theoretical prediction of silicon ADMEs and the toxicity of **Quercetin**, **Quercetagenin**, **Rutin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Axillarin** and Antiviral **Remdesivir** compounds (Lipinski et al., 2001). A Swiss ADME online tool was also used to estimate the Lipinski parameters (Swiss ADME). To predict the biocompatibility and transportation of an active compound through a blood-brain obstacle, the topological polar surface (TPSA) has been cast-off (Ertl et al., 2000). Bioavailability is too multidimensional but mainly concerned with the absorption of the digestive system (Daina et al., 2016). Absorption percentage was determined from the formulas: percent ABS = 109 (TPSA x 0.345). Further predictions involved CYP2D6, P-glycoprotein inhibition, phospholipidosis (PLD), CYP2D9 and water solubility.

RESULTS AND DISCUSSION

In-silico docking

Docking simulations remained carried out to progress kind of the conceivable progression of biological activity. The natural analogues **Quercetin**, **Quercetagenin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin**, as well as Antiviral **Remdesivir**, 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 flavonoid derivative **Volkensiflavone** demonstrates astonishing inhibition capability with inhibition ability of -8.9 kcal/mol over former derivatives **Quercetin** (-7.3kcal/mol), **Quercetagetin** (-7.6 kcal/mol), **Ternatin** (-7.5 kcal/mol), **Melinternatin** (-7.7 kcal/mol), **Formononetin** (-7.0 kcal/mol), **Afromosin** (-6.7 kcal/mol), **Chrysosplenol B** (-7.5 kcal/mol), **Chrysosplenol C** (-7.8 kcal/mol), **Axillarin** (-7.7 kcal/mol) and antiviral drug **Remdesivir** (-7.4 kcal/mol) in 5N5O receptor individually. The ability of hydrogen bonding is an essential aspect of bonding equilibrium between ligand and protein, 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 inhibitors in respective protein remained fewer than 3.5 Å, demonstrating the strong hydrogen link amongst ligands and receptor. **Volkensiflavone** demonstrates two associations between hydrogen bonding and 5N5O receptor. Asn142 and Gln189 amino acid residues were associated with bond lengths of 2.84 and 2.36 Å in contact with hydrogen. The residues of His41, Met49, Ser144, Cys145 and Met165 amino acids came in contact with hydrophobics. **Fig. 2** indicates the hydrophobic and hydrogen bonding interaction of residues of amino acids with compound **Volkensiflavone** in 5N5O protein. The antiviral Remdesivir treatment demonstrates two associations by hydrogen bonding through the 5N5O receptor. The amino acids Cys44 and Glu166 are entangled through associations between hydrogen and the bond lengths 2.20 and 2.49 Å. The amino acid residues Thr25, Met165, Leu167, Pro168 and Gln189, were mixed within hydrophobic encounters. **Fig. 3** indicates the hydrogen and hydrophobic interaction of **Remdesivir** antiviral medication with 5N5O protein. **Table-1** displays the molecular interactions of natural analogues on target protein 5N5O. **Volkensiflavone** natural flavonoid analogue demonstrates impressive inhibition ability through binding energy of -9.0 kcal/mol relative to other compounds **Quercetin** (-7.4 kcal/mol), **Quercetagetin** (-7.6 kcal/mol), **Ternatin** (-7.1 kcal/mol), **Melinternatin** (-7.9 kcal/mol), **Formononetin** (-7.3 kcal/mol), **Afromosin** (-7.0 kcal/mol), **Chrysosplenol B** (-7.4

kcal/mol), **Chrysosplenol C** (-7.4 kcal/mol), **Axillarin** (-7.4 kcal/mol) and antiviral drug **Remdesivir** (-7.7 kcal/mol) in 6LU7 protein individually. Compound **Volkensiflavone** displays three interactions of hydrogen bonding with receptor 6LU7. His41, Met49 and Phe140 were hydrogen bonding amino acid residues with bond lengths of 2.76, 2.96 and 1.86 Å. The amino acid residues Cys145, Met165 and Glu166, have been entangled in hydrophobic encounters. **Fig. 4** demonstrated the bonding of hydrogen and hydrophobic constructions of amino acid residues with **Volkensiflavone** 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 **Fig. 5** of amino acid residues in the 6LU7 protein. The findings revealed that the compound **Volkensiflavone** 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**.

3.2 Molecular property and ADME prediction

The progress of bioactive components as healers is driven by high oral bioavailability (Newby *et al.*, 2015). The key forecasters of this analysis demonstrated, for example, the low polar surface region, hydrogen bonding ability, decreased molecular versatility and intestinal absorption (Azam *et al.*, 2012). The natural antiviral analogues **Quercetin**, **Quercetagetin**, **Ternatin**, **Melinternatin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin** agrees Lipinski's "Rule of 5" with 0 infringement and compounds **Volkensiflavone** and **Remdesivir** Fails "Rule of 5" with two infringement HBA, MW>500, HBD and RoB (**Table-3**). The molecular conformational changes were defined by the number of revolving ties and the potential for the receptor binding. The compounds **Quercetin**, **Quercetagetin**,

Volkensiflavone, **Ternatin**, **Meliternatin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin** 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 property of tPSA (topological Polar Surface Area) revealed the passive molecular transport across membranes and blood-brain barrier penetration (Ertl *et al.*, 2000). Checked substances except for compounds **Quercetagetin**, **Volkensiflavone**, and **Remdesivir** with

tPSA values $< 140 \text{ \AA}^2$ fulfil the requirements for subsequent oral administration for gastrointestinal absorption. In comparison, all of the compounds studied except for **Quercetin** (tPSA = 131.36 \AA^2), **Quercetagetin** (tPSA = 151.59 \AA^2), **Volkensiflavone** (tPSA = 177.89 \AA^2), **Ternatin** (tPSA = 107.59 \AA^2), **Chrysosplenol B** (tPSA = 107.59 \AA^2), **Chrysosplenol C** (tPSA = 118.59 \AA^2), **Axillarin** (tPSA = 129.59 \AA^2), and **Remdesivir** (tPSA = 213.36 \AA^2) have lower blood-brain barrier (tPSA $> 90 \text{ \AA}^2$), which reveals detrimental possessions of Central nervous system (CNS).

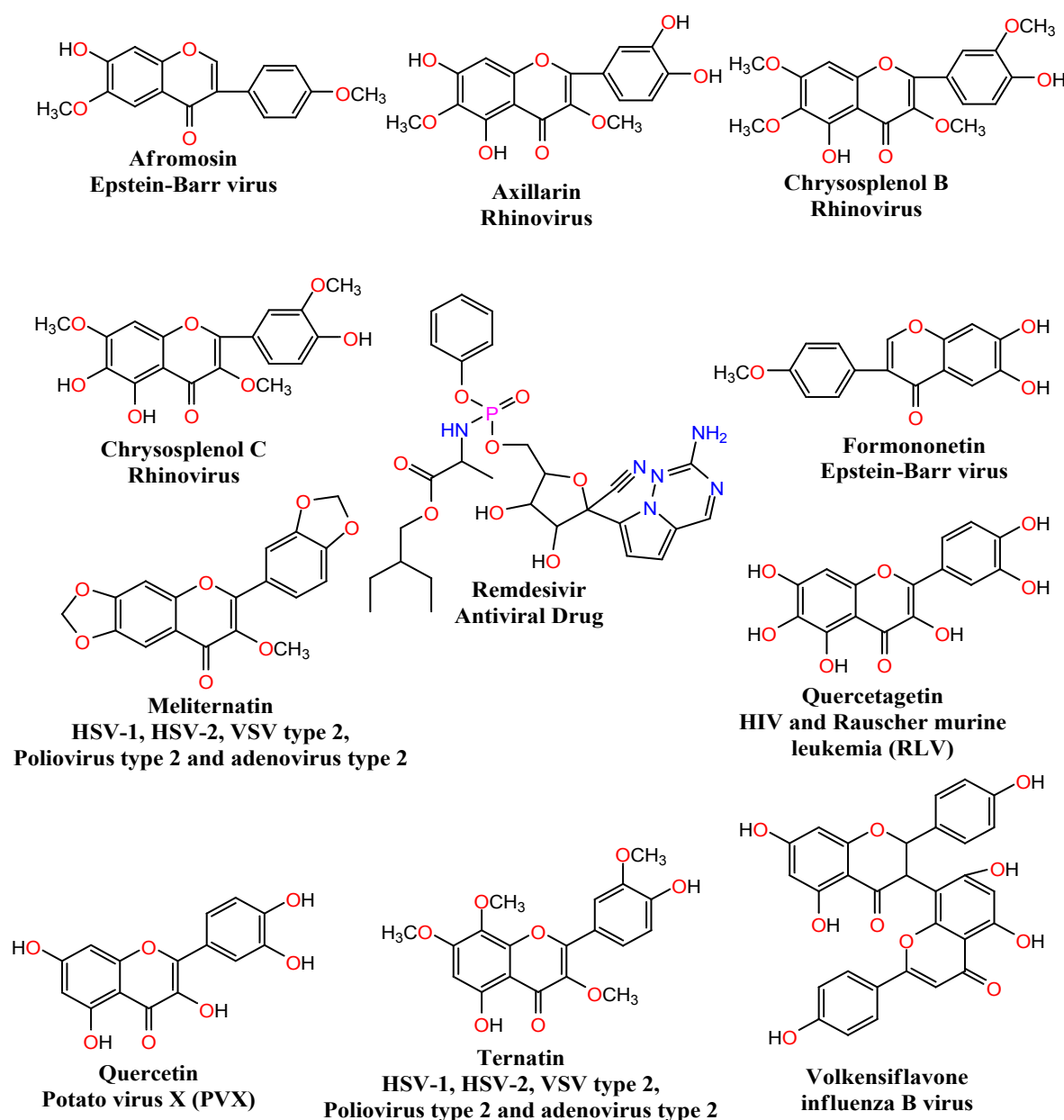


Figure 1. Natural antiviral derivatives

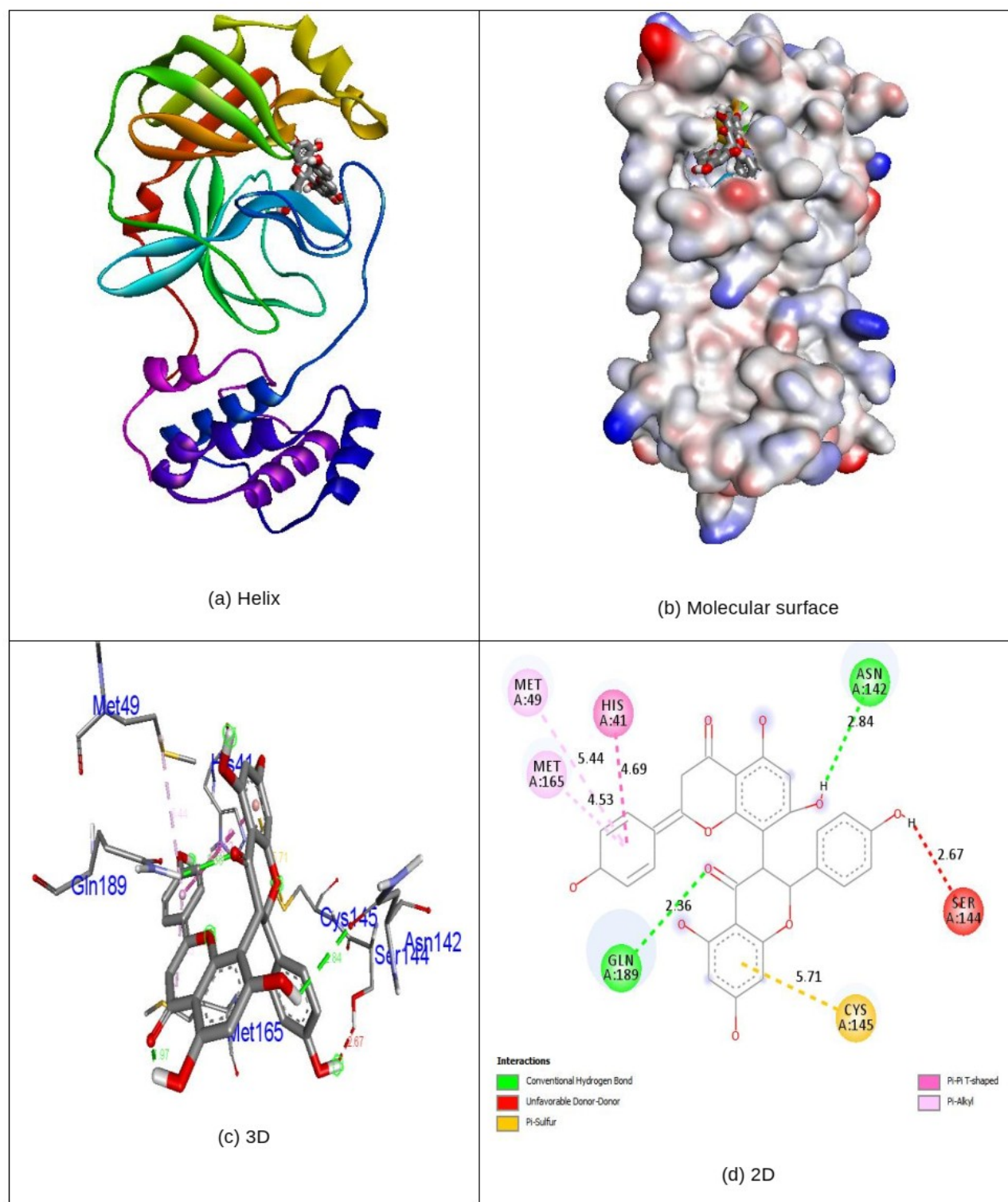


Figure 2. Interactions of **Volkensiflavone** inside the binding pocket of 5N5O protein.

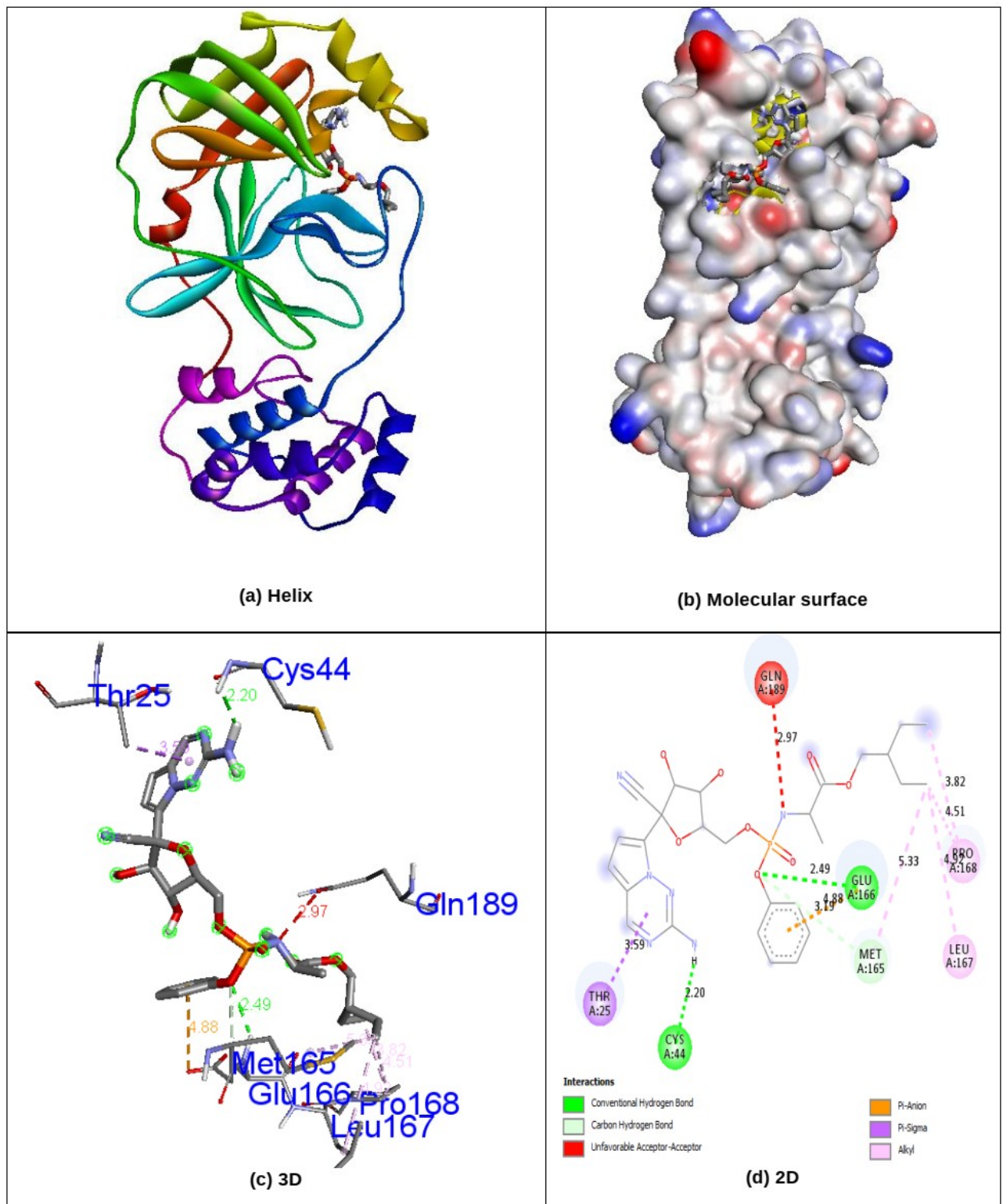


Figure 3. Interactions of antiviral drug Remdesivir inside the binding pocket of 5N5O protein.

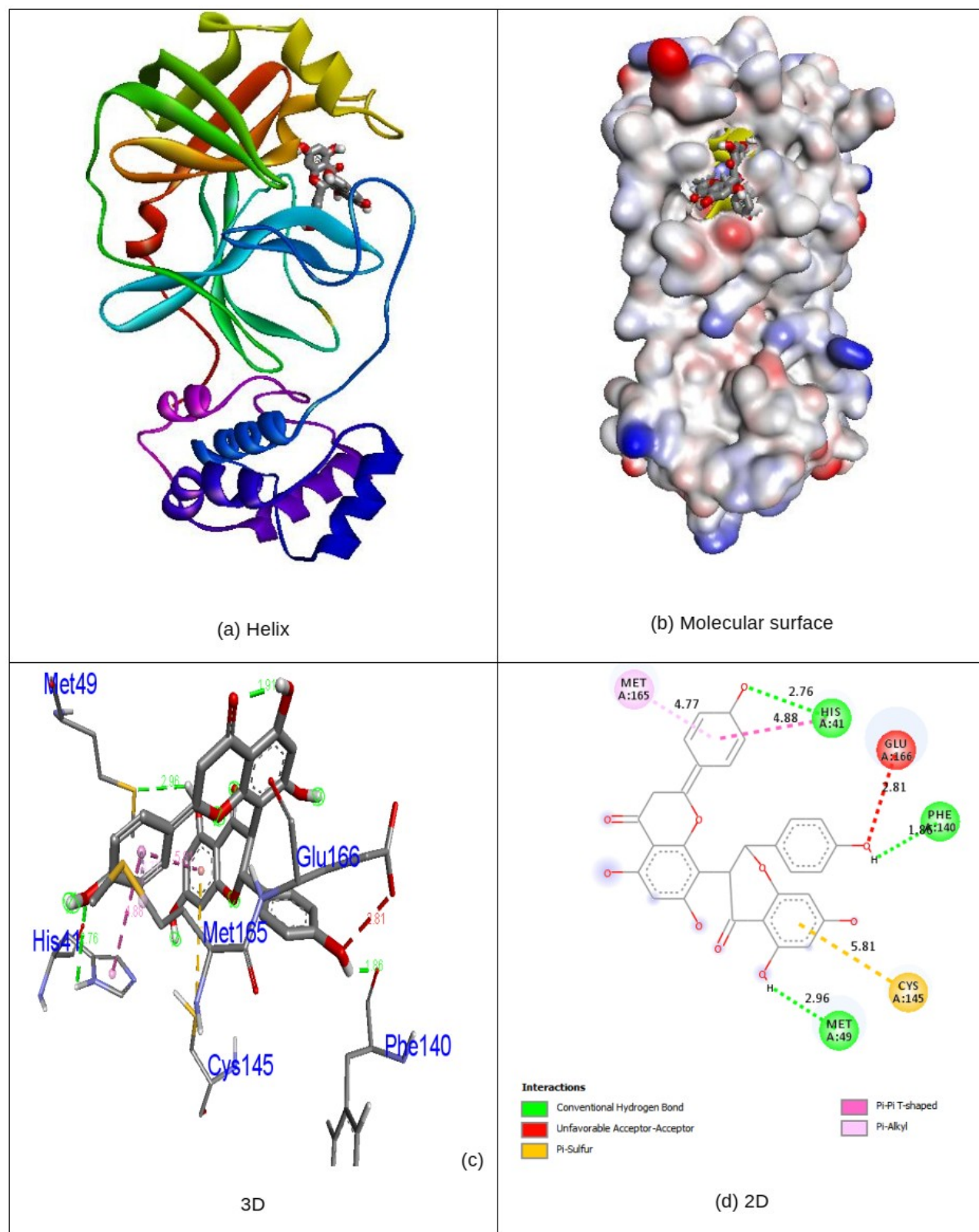


Figure 4. Interactions of Volkensi flavones inside the binding site of 6LU7 protein.

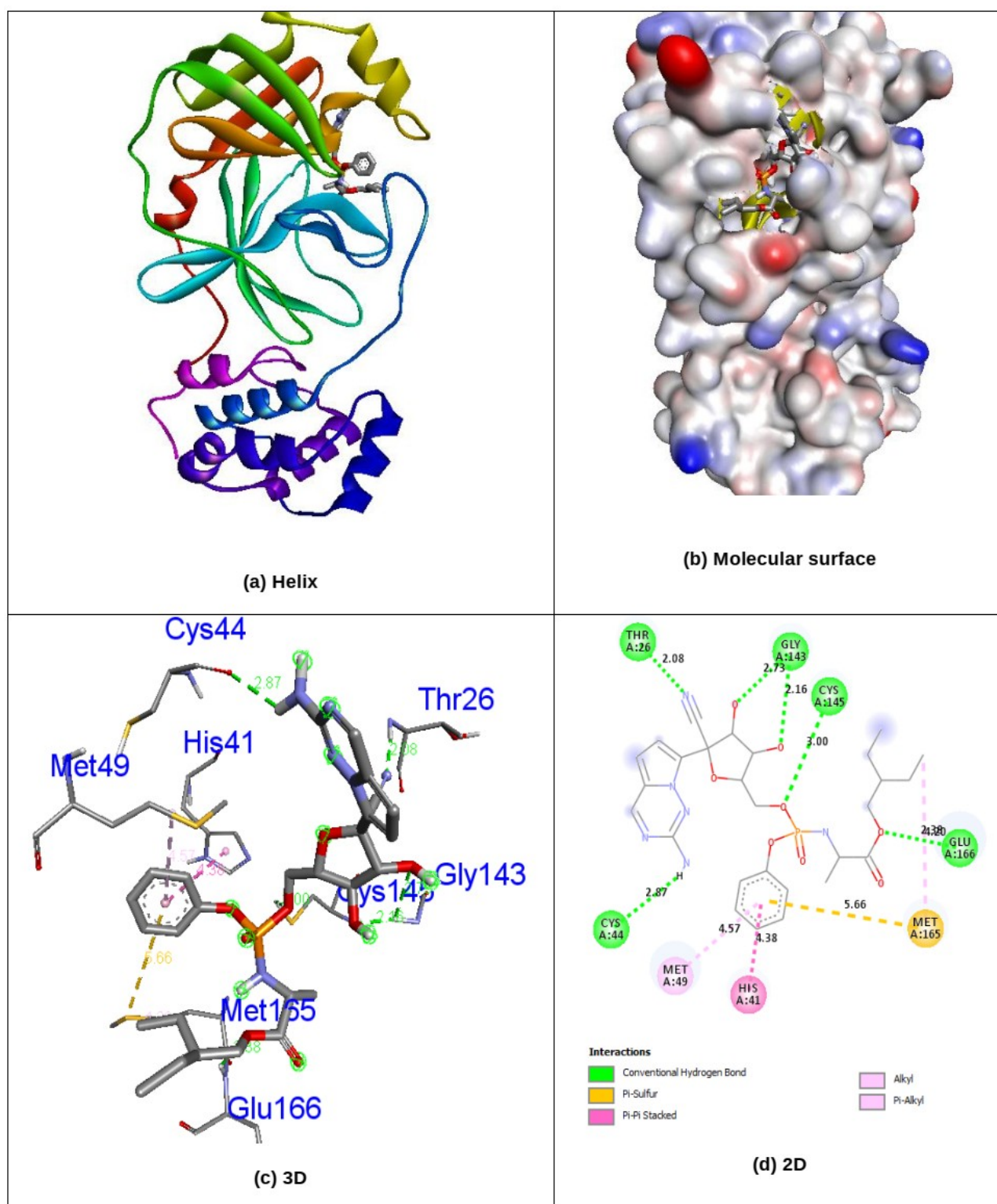


Figure 5. Interactions of antiviral drug Remdesivir inside the binding pocket of 6LU7 protein.

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

Inhibitors	Binding energy (kcal/mol)	Number of H-bonds	Hydrogen bonding residues
Quercetin (1a)	-7.3	3	Leu141, Cys145, Glu166
Quercetagenin (1b)	-7.6	3	Gly143, Ser144
Volkensiflavone (1c)	-8.9	2	Asn142, Gln189
Ternatin (1d)	-7.5	2	Gly143, Cys145
Meliteratin (1e)	-7.7	0	-
Formononetin (1f)	-7.0	2	Asn142, Arg188
Afromosin (1g)	-6.7	2	Asn142, Gln189
Chrysosplenol B (1h)	-7.5	1	Gly143
Chrysosplenol C (1i)	-7.8	3	Gly143, Cys145
Axillarin (1j)	-7.7	5	Leu141, Gly143, Ser144, Cys145
Remdesivir (1k)	-7.4	2	Cys44, Glu166

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

Inhibitors	Binding energy (kcal/mol)	Number of H-bonds	Hydrogen bonding residues
Quercetin (1a)	-7.4	0	-
Quercetagenin (1b)	-7.6	3	Met49, Leu141, Asn142
Volkensiflavone (1c)	-9.0	3	His41, Met49, Phe140
Ternatin (1d)	-7.1	3	Ser46, Leu141, Cys145
Meliteratin (1e)	-7.9	1	Gly143
Formononetin (1f)	-7.3	1	Asn142
Afromosin (1g)	-7.0	1	Phe140
Chrysosplenol B (1h)	-7.4	4	Gly143, Ser144, Cys145
Chrysosplenol C (1i)	-7.4	4	Ser46, Leu141, Cys145
Axillarin (1j)	-7.4	2	His41, Thr190
Remdesivir (1k)	-7.7	6	Thr26, Cys44, Gly143, Cys145, Glu166

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.

Table 3 Molecular property prediction and Virtual ADME (absorption, distribution, metabolism, excretion) of the potent compounds (1a-1k).

Comp.	tPSA ^a	%Abs ^b	MW ^c	RoB ^d	HBD ^e	HBA ^f	MR ^g	llogP ^h (MlogP)	LogS ⁱ	CYP2D6 Inhibitor
Rule	≤140 Å ²	>50	≤500	≤10	≤5	≤10	40–130	<5	>-4	-
Quercetin (1a)	131.36	63.68	302.24	1	5	7	78.03	1.63 (-0.56)	-3.16	Yes
Quercetagetin (1b)	151.59	56.70	318.24	1	6	8	80.06	1.73 (-1.08)	-3.01	No
Volkensiflavone (1c)	177.89	47.62	540.47	3	6	10	143.60	2.19 (0.41)	-6.55	No
Ternatin (1d)	107.59	71.88	374.34	5	2	8	97.93	3.41 (-0.12)	-4.24	No
Meliteratin (1e)	76.36	82.65	340.28	2	0	7	86.54	3.29 (0.98)	-4.18	Yes
Formononetin (1f)	79.90	81.43	284.26	2	2	5	78.46	2.39 (0.77)	-3.57	Yes
Afromosin (1g)	68.90	85.22	298.29	3	1	5	82.93	2.97 (1.01)	-3.77	Yes
Chrysosplenol B (1h)	107.59	71.88	374.34	5	2	8	97.93	3.35 (-0.12)	-4.24	No
Chrysosplenol C (1i)	118.59	68.08	360.31	4	3	8	93.46	2.90 (-0.35)	-4.02	Yes
Axillarin (1j)	129.59	64.29	346.29	3	4	8	89.00	2.37 (-0.59)	-3.81	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 tested compounds demonstrated absorption percentage (percentage Abs = > 50), suggesting strong bioavailability except **Volkensiflavone** (% Abs = 47.62) and **Remdesivir** (% Abs = 35.39). Bioavailability by oral route was appropriate (> 50 percent). The compounds **Quercetin**, **Quercetagetin**, **Formononetin**, **Afromosin** and **Axillarin** were very water-soluble (-logS > -4) excluding compounds **Volkensiflavone** (-logS -6.55), **Ternatin** (-logS -4.24) **Meliteratin** (-logS -4.18), **Chrysosplenol B** (-logS -4.24), **Chrysosplenol C** (-logS -4.02), and **Remdesivir** (-logS -4.12) have moderate water solubility. The side effects of liver impairment doesn't suspected in the case of compounds **Quercetagetin**, **Volkensiflavone**, **Ternatin**, **Chrysosplenol B** and **Remdesivir** since they were predicted to be CYP2D6 non-inhibitors. A part of the P-gp (P-glycoprotein) family transporter ATP-binding cassette (ABC) comprises the intestinal absorption,

brain penetration and pharmaceutical metabolism; the aforementioned caginess may significantly modify the bioavailability and defence of the drug (Fromm *et al.*, 2000). Phospholipidosis convinced medication is a condition known for the further growth of phospholipids in flesh and medication-related poisonousness (Nonoyama *et al.*, 2008). The findings indicate that the studied compounds **Quercetin**, **Quercetagetin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin** were not a part of P-gp substrate and phospholipidosis was not promoted. The checks for P-gp-phospholipidosis was anticipated only in **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 compounds were **Meliteratin** and **Afromosin**. All tested compounds assessed were recognised by way of drug-like and

passed "Rule of 5" of Lipinski except compounds **Volkensiflavone** and **Remdesivir**. The restrictions predicted are all within the context of accepted principles.

CONCLUSION

COVID-19 has arisen in the humanoid community, in China, and is a possible risk to healthiness internationally. However, there is not at all precisely approved medication to delight the situation and the already accessible COVID-19 medicines coping with essential protease. The goal of the current study was to inspect some natural analogues extracted from medicinal plants that might remain tossed off to combat COVID-19. The utmost frequently proposed compounds in healing plants that may function as important COVID-19 inhibitors of key protease (PDB ID: 5N5O, 6LU7) were **Quercetin**, **Quercetagenin**, **Volkensiflavone**, **Ternatin**, **Meliteratin**, **Formononetin**, **Afromosin**, **Chrysosplenol B**, **Chrysosplenol C** and **Axillarin** with negative binding energies. Studies in molecular docking have revealed that natural flavonoid derivative **Volkensiflavone** displayed exceptional inhibition with a binding energy value of -8.9,-9.0kcal/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, the advance study is necessary to inspect the possible application of these compounds in medicinal plants.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

- Abo-Zeid, Y., Ismail, N. S., McLean, G. R., & Hamdy, N. M. (2020). A molecular docking study repurposes FDA approved iron oxide nanoparticles to treat and control COVID-19 infection. *European Journal of Pharmaceutical Sciences*, 153, 105465.
- Amin, S. A., & Jha, T. (2020). Fight against novel coronavirus: a perspective of medicinal chemists. *European Journal of Medicinal Chemistry*, 201, 112559.
- Azam, F., Madi, A. M., Ali, H. I., (2012). Molecular Docking and Prediction of Pharmacokinetic Properties of Dual Mechanism Drugs that Block MAO-B and Adenosine A2A Receptors for the Treatment of Parkinson's Disease. *J. Young Pharm.*, 4, 184-192.
- Beladi, I., Pusztai, R., Mucsi, I., Bakay, M., Gabor, M., (1977). Activity of some flavonoids against viruses. *Ann N Y Acad Sci.*, 284, 358-364.
- Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., Chen, S., Wang, Z., Zhang, Z., Cao, R., Zhong, W., Liu, Y., Liu, L., (2020). Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering (Beijing)*, 6(10), 1192-1198.
- Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., Wagstaff, K.M., (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Res.*, 178, 104787.
- Choy, K.-T., Wong, A. Y.-L., Kaewpreedee, P., Sia, S. F., Chen, D., Hui, K. P. Y., Chu, D. K. W., Chan, M. C. W., Cheung, P. P.-H., Huang, X., Peiris, M., Yen, H.-L., (2020). *In vitro* evaluation of antiviral activity of single and combined repurposable drugs against SARS- CoV-2. *Antiviral Res.*, 178, 104786.
- Cody, V., Middleton, E., Harborne, J. B., Beretz, A., eds (1988). *Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular and Medicinal Properties*. Alan R. Liss, Inc., New York.
- Daina, A., Zoete, V., (2016). A Boiled-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *Chem. Med. Chem.*, 11, 1117-1121.
- Derwand, R., Scholz, M., (2020). Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?. *Med. Hypotheses.*, 142, 109815.
- Dong, L., Hu, S., Gao, J., (2020). Discovering drugs to

- treat coronavirus disease 2019 (COVID- 19). *Drug Discover. Therapeu.*, 14, 58-60.
- Du, Y.X., Chen, X.P., (2020). Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. *Clin Pharmacol Ther.*, 108, 242-247.
- Elfiky, A. A., (2020). Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Science.*, 248, 117477.
- Elfiky, A. A., (2020a). Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Science.*, 253, 117592.
- Ertl, P., Rohde, B., Selzer, P., (2000). Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.*, 43, 3714-3717.
- French, C. J., Towers, N., (1992). Inhibition of infectivity of potato virus X by flavonoids. *Phytochemistry.*, 31, 3017-3020.
- Fromm, M. F., (2000). P-glycoprotein: A defense mechanism limiting oral bioavailability and CNS accumulation of drugs. *Int. J. Clin. Pharmacol. Ther.*, 38, 69-74.
- Goyal, B., Goyal, D., (2020). Targetting the Dimerization of the Main Protease of Coronaviruses: A Potential Broad-Spectrum Therapeutic Strategy. *ACS Comb. Sci.*, 22, 297-305.
- Guerriero, G., Berni, R., Armando Munoz-Sanchez, J., Apone, F., Abdel-Salam, E. M., Qahtan, A. A., Alatar, A. A., Cantini, C., Cai, G., Hausman, J. F., Siddiqui, K. S., Sotomayor, S. M. T. H., Faisal, M., (2018). Production of plant secondary metabolites: Examples, tips and suggestions for biotechnologists. *Genes (Basel).*, 9, 34-46.
- Hui, D. S., Azhar, E. I., Madani, T. A., Ntoumi, F., Kock, R., Dar, O., Ippolito, G., Mchugh, T. D., Memish, Z. A., Drosten, C., Zumla, A., Petersen, E., (2020). The continuing 2019- nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int. J. Infec. Dis.*, 91, 264-266.
- Jiang, S., Du, L., Shi, Z., (2020) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. *Emerg. Microbes Infect.*, 9, 275-277.
- Jo, S., Kim, S., Shin, D. H., Kim, M. S., (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *J. Enzyme Inhib. Med. Chem.*, 35, 145-151.
- Konoshima, T., Kozuka, M., Haruna, M., Ito, K., Kimura, T., Tokuda, H., (1989). Studies on the constituents of Leguminous plants. XII. The structure of new triterpenoids saponins from *Wistaria brachybotrys*. *Sieb Chem Pharm Bull.*, 37, 2731-2735.
- Li, J.-Y., You, Z., Wang, Q., Zhou, Z.-J., Qiu, Y., Luo, R., Ge, X.-Y., (2020). The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. *Microbes Infect.*, 22, 80-85.
- Lin, Y., Anderson, H., Flavin, M., Pai, Y., (1997). *In vitro* anti-HIV activity of biflavonoids isolated from *Rhus succedanea* and *Garcinia multiflora*. *J Nat Prod.*, 60, 884-888.
- Lipinski, C. A., Lombardo, F., Dominy B. W., Feeney P. J., (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.*, 46, 3-26.
- Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., Wang, M., (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. *Cell Discov.*, 6, 16.
- Manisha Y., Swasti D., Satya E.J., (2020). Emerging strategies on in silico drug development against COVID-19: challenges and opportunities. *Eur. J. Pharm. Sci.*, 155, 105522.
- Newby, D., Freitas, A. A., Ghafourian, T., (2015). Decision trees to characterize the roles of permeability and solubility on the prediction of oral absorption. *Eur. J. Med. Chem.*, 90, 751-65.
- Nonoyama, T., Fukuda, R., (2008). Drug induced

- phospholipidosis pathological aspects and its prediction. *J. Toxicol. Pathol.*, 21, 9-24.
- Ojha, R., Gupta, N., Naik, B., Singh, S., Verma, V. K., Prusty, D., & Prajapati, V. K. (2020). High throughput and comprehensive approach to develop multiepitope vaccine against minacious COVID-19. *European Journal of Pharmaceutical Sciences*, 151, 105375.
- Shannon, A., Le, N. T.-T., Selisko, B., Eydoux, C., Alvarez, K., Guillemot, J.-C., Decroly, E., Peersen, O., Ferron, F., Canard, B., (2020). Remdesivir and SARS-CoV-2: Structural requirements at both nsp 12 RdRp and nsp 14 Exonuclease active-sites. *Antiviral Research.*, 178, 104793.
- Shiraki, K., Daikoku, T. (2020). Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther.*, 209, 107512.
- Simoës, C. M., Girre, M., Gleye, J., Fauvel, M., (1990). Antiviral activity of ternatin and meliternatin 3-methoxyflavones from species of *Rutaceae*. *J Nat Prod.*, 53, 989-992.
- Swiss ADME. Available online: <http://www.swissadme.ch>
- Taha, M., Ismail, N. H., Khan, A., Shah, S. A. A., Anwar, A., Halim, S. A., Fatmi, M. Q., Imran, S., Rahim, F., Kha, K. M., (2015). Synthesis of novel derivatives of oxindole, their urease inhibition and molecular docking studies. *Bioorg. Med. Chem. Let.*, 25, 3285-3289.
- Thayil, S. M., & Thyagarajan, S. P. (2016). Pa-9: A flavonoid extracted from *Plectranthus amboinicus* inhibits HIV-1 protease. *Int. J. Pharmacogn. Phytochem. Res*, 8(6), 1020-1024.
- Trott, O., Olson, A. J., (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem.*, 31, 455-61.
- Tsuchiya, Y., Shimizu, M., Himaya, Y., Itoh, K., Hashimoto, Y., Nakayama, M., Horie, T., Morita, N., (1985). Antiviral activity of natural occurring flavonoids *in vitro*. *Chem Pharm Bull.*, 33, 3881-3886.
- Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., Xiao, G., (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res.*, 30, 269-271.
- Wang, X., Cao, R., Zhang, H., Liu, J., Xu, M., Hu, H., Li, Y., Zhao, L., Li, W., Sun, X., Yang, X., Shi, Z., Deng, F., Hu, Z., Zhong, W., Wang, M., (2020). The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 *in vitro*. *Cell Discov.*, 6, 28.
- Yang, L., Wen, K. S., Ruan, X., Zhao, Y. X., Wei, F., Wang, Q., (2018). Response of plant secondary metabolites to environmental factors. *Molecules.*, 23, 1-26.
- Yin, W., Mao, C., Luan, X., Shen, D.-D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y.-C., Tian, G., Jiang, H.-W., Tao, S.-C., Shen, J., Jiang, Y., Jiang, H., Xu, Y., Zhang, S., Zhang, Y., Xu, H. E., (2020). Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. *Science.*, 368, 1499-1504.
- Zakaryan, H., Arabyan, E., Oo, A., Zandi, K., (2017). Flavonoids: promising natural compounds against viral infections. *Arch. Virol.*, 162, 2539-2551.