Kolaviron (Kolaflavanone), apigenin, fisetin as potential Coronavirus inhibitors: *In silico* investigation

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Abstract

The outbreak of COVID-19 caused by SARS-CoV-2 is increasing with an alarming rate of associated frightening mortality without no known approved therapy. The emergence of new infectious diseases and increase in frequency of drug resistant viruses demand effective and novel therapeutic agents. This study investigated the putative inhibitory potentials of apigenin, fisetin, kolaflavanone, and remdesivir towards SARS-COV2 major protease (6LU7) using in silico methods. Pharmacodynamics, pharmacokinetics and toxicological profiles of the compounds were also examined using the pkCSM server. All the compounds showed good affinity to the binding pocket of 6LU7. It was observed that kolaflavanone exhibited the highest binding affinity when compared to apigenin, fisetin, and remdesivir. The amino acids ASN238, TYR237, LEU286, and LEU287 were showed as the key residues for kolaflavanone binding to human SARS-COV2 major protease. The Pharmacodynamics and pharmacokinetics results suggested that all the tested compounds have significant drug likeness properties and they could be absorbed through the human intestine. Additionally, all the tested compounds except remdesivir are not hepatoxic and also displayed non or relatively low toxic effects in human. Summarily, the results of this study indicated that all the tested compounds are potential putative inhibitors of SARS-COV2 major protease with no or low toxicity effects. However, further experimental and clinical studies are needed to further explore their activities and validate their efficacies against COVID-19.

Introduction

Novel Coronavirus disease 2019 (COVID-19), ranked among the ninth deadliest world pandemic, is a highly infectious and severe acute respiratory disorder caused by a morbific virus called SARS-CoV-2 which is transmitted to humans via contact with infected persons and/or feeding on infected animals. The COVID-19 clinical manifestations are very similar to viral pneumonia and include fever, fatigue, cough, shortness of breath, and other complications. According to reports obtained on WHO and NCDC websites as of 27th June 2020, the coronavirus breakout in Wuhan, a city in Hubei Province of China in November 2019 and has spread to many countries in the world. This global pandemic has forced many nations to lock down their social and economic activities which in turn have adverse effects on the economy. Globally, more than ten million people have been confirmed infected with over 500,000 deaths. Nigeria is one of the countries seriously affected by the virus having over 25,000 cases and more than 500 mortalities [1,2]. Thus, there is an exigent need for effective and non-invasive treatment.

Coronaviruses (SARS-CoV) are non-segmented positive-sense single-stranded RNA viruses with a large viral RNA genome of diameter 80–120 nm (figure 1). They belong to the family of Coronaviridae, in the subfamily Orthocoronaviridae which consists of four genera namely: Alpha, Beta, Gamma, and Delta coronavirus [3]. Some of the modes of actions of SARS-CoV-2 include hyper-inflammation characterized by a sudden and fatal hyper-cytokinaemia with multi-organ failure [4]; immunosuppression; reduction of Angiotensin-Converting Enzyme 2 (ACE2) to enhance pulmonary vascular permeability and damage the alveoli [5]; and activated by ORF3a, ORF3b, and ORF7a via JNK pathway which induces lung damage [6].

At present, there is no known effective treatment or vaccine that can mitigate/inhibit coronavirus. Available clinical interventions for COVID-19 are only palliative and limited to support. Therefore, many research groups around the world are currently focusing on developing novel treatments such as vaccines and antivirals. This research investigated the inhibitory potentials of some naturally occurring phytochemicals against COVID-19 major protease (6LU7). These phytochemicals can be repurposed to mitigate the pathogenesis of the SARS-CoV-2 and thus put an end to the frightening associated mortality rate.

Materials And Methods

Protein preparation

The crystal structure of SARS-COV2 major protease (6LU7) was retrieved from the protein databank (www.rcsb.org). Prior to docking and analysis, the crystal structure was prepared by removing existing ligands and water molecules. Also, missing hydrogen atoms were added using Autodock v4.2 program, Scripps Research Institute. Thereafter, non-polar hydrogens were merged while polar hydrogen was added and subsequently saved into pdbqt format in preparation for molecular docking.

Ligand preparation

The SDF structures of apigenin, fisetin, kolaflavanone, and remdesivir were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov). The compounds were converted to mol2 chemical format. Polar hydrogens were added while non-polar hydrogens were merged with the carbons and the internal degrees of freedom and torsions were set. The protein and ligand molecules were further converted to the dockable PDBQT format using Autodock tools.

Molecular docking

Docking of the ligands to the targeted protein and determination of binding affinities was carried out using AutodockVina [7]. The PDBQT formats of the receptor and that of the ligands were positioned at their respective columns and the software was run. The binding affinities of compounds for the protein target were recorded. The compounds were then ranked by their affinity scores. The molecular interactions between the receptor and compounds with most remarkable binding affinities were viewed with Discovery Studio Visualizer, BIOVIA, 2016. The respective binding free energy was calculated by the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) using HawkDock Server (http://cadd.zju.edu.cn/hawkdock/).

Molecular dynamics simulation

The conformational stability of the protein-ligand interactions was evaluated using molecular dynamics simulations analysis performed through iMODS server (http://imods.chaconlab.org) by normal mode analysis (NMA) predicting properties such as deformability, mobility profiles, eigenvalues, variance, co-variance map and elastic network of the protein-ligand interactions [8].

ADMET analysis

The solubility, pharmacodynamics, pharmacokinetics and toxicological profiles of apigenin, fisetin, kolaflavanone, and remdesivir were computed based on their ADMET (absorption, distribution, metabolism, elimination, and toxicity) studies using pkCSM tool (http://biosig.unimelb.edu.au/pkcsm/prediction) as described by Pires et al., (2015). The canonical SMILE molecular structures of the compounds used in the studies were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

Results

Molecular docking analysis

The molecular docking analysis and visualization of 6LU7 binding with apigenin, fisetin, kolaflavanone, and remdesivir is shown in figure 1. Out of the four compounds, kolaflavanone displayed the best docked score (-7.2 kcal/mol) with the SARS-COV2 major protease (6LU7). ASN238, TYR237, LEU286, and LEU287 amino acid residues participating in the interaction at the binding pocket of the SARS-COV2 major protease (6LU7) (figure 1C). Fisetin exhibited (-7.0 kcal/mol) binding affinity with 6LU7. ARG131, THR199, LEU286, and LEU287 amino acid residues participating in the interaction at the binding pocket of 6LU7 (figure 1B). Apigenin showed (-6.7 kcal/mol) binding affinity with 6LU7. LEU286, and LEU287 amino acid residues participating in the interaction at the binding pocket of 6LU7 (figure 1A). Remdesivir exhibited (-6.6 kcal/mol) binding affinity with 6LU7. ARG131, THR199, LYS137, ASP289, LEU272, LEU287, and MET276 amino acid residues participating in the interaction at the binding pocket of 6LU7 (figure 1D).

Molecular properties of the phytochemicals

Data in table 2 revealed the results of the molecular properties of the phytochemicals used in this study. Remdesivir was found to have the highest molecular weight of 602.585, while that of kolaflavanone is 588.521, fisetin is 286.239 and apigenin is 270.24. Similarly, the surface area of the compounds: Remdesivir, kolaflavanone, fisetin, and apigenin are 242.488, 242.369, 117.519 and 112.519 respectively. Kolaflavanone has the highest lipophilicity of 3.7063, apigenin has 2.5768, while fisetin has the least lipophilicity of 2.2824.

Predicted absorption properties of the phytochemicals

The predicted absorption properties of each of the compounds were reported in table 3. The result showed that kolaflavanone has the highest water solubility value of -2.9 while apigenin has the lowest valve of -3.329. Apigenin has the highest permeability of 1.007, with fisetin having the least permeability valve of 0.058. All the compounds are substrate of P-glycoprotein. Only kolaflavanone and remdesivir are inhibitors of P-glycoprotein-I while kolaflavanone is the only inhibitor of P-glycoprotein-II.

Predicted *in vivo* distribution and cytochrome P450 promiscuity of the phytochemicals

Table 4 showed the predicted *in vivo* distribution of the compounds. All the compounds tested have relatively low steady-state volume of distribution. Also, the predicted result revealed that kolaflavanone has the highest unbound fraction in the human blood. All the compounds have relatively low blood-brain barrier and CNS permeability values.

Table 5 displayed the predicted human cytochrome P450 promiscuity of the screened compounds. All the compounds are not substrate of CYP2D6 and CYP3A4 expected remdesivir which is predicted to be CYP3A4 substrate. Similarly, none of the compounds is an inhibitor of CYP2D6 and CYP3A4. Only apigenin is an inhibitor of CYP2C19 and fisetin as inhibitor of CYP2C9.

Predicted *in vivo* clearance of the phytochemicals

The predicted clearance of each of the compounds were reported in table 6. Apigenin has the highest total clearance rate of 0.566 while kolaflavanone has the least clearance rate of -0.359. Likewise, only kolaflavanone is substrate of renal organic cation transporter.

Predicted toxicological profile of the phytochemicals

Table 7 reported the predicted toxicological profile of all the tested compounds. None of the compounds has mutagenic potentials against bacteria (AMES toxicity), nor has potential dermal adverse effects and they are human ether-a-go-go-related gene (hERG I) inhibitors. All the compounds have relatively low maximum recommended tolerated dose except fisetin having valve (0.579) greater than recommended value of 0.477 (log mg/kg/day). Likewise, all the compounds are non-hepatotoxic except remdesivir.

Discussion

Virtual screening and molecular docking are vital methods use in drug repurposing approach to fast track drug discovery and appropriate therapeutic interventions in a pandemic situation. They elucidate the mechanism of ligand binding and discover potent inhibitors for targeted proteins. In this study, kolaflavanone showed the best docked score (-7.2 kcal/mol) with the SARS-COV2 major protease (6LU7). The binding energy suggests the affinity of a specific ligand and the strength by which the compound interacts with and bind to the pocket of the target proteins. The scoring value with a lower binding energy (or high docking score) suggests it as a possible drug candidate.

Kolaflavanone (kolaviron) is the most abundant Garcinia bioflavonoids in *Garcinia kola* Heckel (Guttiferae) (Farombi et al., 2019). It is popular for the treatment of malaria, hepatitis, neurodegenerative disease, male sexual dysfunction, and immune-destructive diseases [9,10]. It also protects against the oxidation of lipoprotein [11]. *Garcinia kola* is also used to relieve cold and cure laryngitis [12]. kolaviron has been documented to effectively delay the development of clinical symptoms and and suppresses mortality associated with influenza virus [13]. Experimental studies have proven the antioxidative, anti-inflammatory, anti-apoptotic and modulatory effects of kolaflavanone which could be helpful to inhibit the pathogenesis of COVID-19.

Apigenin (4',5,7-trihydroxyflavone) is one of the most studied phenolics and it is the most widely distributed flavonoids in the plant kingdom. Apigenin is chiefly present herbs (thyme, oregano, chamomile, basil), in vegetables (celery, parsley, onions), plant-based beverages (beer, tea, and wine) and fruits (oranges). It is also found in abundance in Artemisia, Achillea, Matricaria, and Tanacetum [14]. Apigenin has been reported to have anti-diabetic and anticancer properties, also, its beneficial role in amnesia, Alzheimer's Disease, depression and insomnia treatment has been well documented [14].

Fisetin (3,3',4',7-tetrahydroxyflavone), a pigment flavonol also abundant in strawberry, grapes, persimmon, apples, lotus root, onions, peach, tomatoes, and cucumbers. It is also a senolytic agent, as it selectively induces death of senescent cells to alleviate age-related diseases [15]. Fisetin has been reported to have anticancer, antioxidant, anti-inflammatory, anti-apoptotic properties [16].

The results of the solubility, pharmacodynamics, pharmacokinetics and toxicological profiles of apigenin, fisetin, kolaflavanone, and remdesivir are presented in Tables 2–7. The profiles were investigated as a systemic virtual screening of drugs and potential drugs. This is done as alternative to *in vivo* examinations which are essential complements in drug discovery. The Lipinski's rule is a major criterion to evaluate drug likeliness and to determine if a compound with a particular pharmacological and biological actions has physical and chemical properties that could favour its activities in human. The molecular properties of the compounds based on the computed partition coefficient (log P) showed that the compounds have relatively good lipophilicity as the logP values were less than 5 [17,18]. All the tested compounds could be maintained in the system at appropriate concentrations.

Intestinal absorption and Caco2 permeability are indicators that determine the ultimate bioavailability of the drug candidates. The tested compounds (apigenin, fisetin, kolaflavanone, and remdesivir) have relatively low Caco2 permeability potential ($<8\times10^{-6}$ cm/s) and could be absorbed through the human intestine [19]. However, ADMETSAR1 as predicted that remdesivir is subcellular localization in the lysosome [20]. Furthermore, the observed lipophilicities have an association with Caco2 permeability but correlated negatively with water solubility potentials of the tested compounds. This result is in tandem with the findings of Yazdanian et al [21] who used the human colon adenocarcinoma (Caco-2) cell line assay to document no correlation between the drug permeability and measured lipophilicity. All the tested compounds were predicted to be substrates of P-glycoprotein, a member of the ATP-binding cassette transporter and an efflux membrane transporter found chiefly in epithelial cells. On the other hand, kolaflavanone and remdesivir were predicted as P-glycoprotein inhibitors. This indicate that they could modulate the normal physiological activities of P-glycoprotein including restricting the active uptake and the distribution of drugs [22].

The volume of distribution calculated using a steady-state volume of distribution (VDss) as predicted showed that kolaflavanone has the lowest theoretical dose required for uniform distribution in the plasma when compared with other tested compounds (apigenin, fisetin, and remdesivir). VDss showed the distribution of drug in the tissue and plasma. The degree of diffusing across plasma membrane increases in this order remdesivir <apigenin<fisetin < kolaflavanone measured as the fraction that is in the

unbound state. The predicted evaluation on the nervous system distribution of the compounds revealed that lipophilicity of the compounds correlates to the degree of permeability across the central nervous system and the blood-brain barrier.

Cytochrome P450 is a group of enzymes that perform crucial functions in drug metabolism. They play a major role in the activation of drugs and also in the toxicity effects of the drugs. Only remdesivir is substrate of CYP3A4, all other tested compounds were neither substrate of CYP2D6 nor CYP3A4. The lipophilicity of the drug appears to correlate negatively to metabolism-related toxicity. Furthermore, only kolaflavanone was a substrate of renal organic cation transporter, this implies that other tested compounds are possibly cleared through other available routes such as sweat, bile, etc. Also, kolaflavanone was observed to have the least total clearance while apigenin has the highest. Drug clearance is related to bioavailability and is crucial for determining dosing rates to achieve steady-state concentrations.

The toxicological assessment of the tested compounds revealed that all the tested compounds expect remdesivir are not hepatoxic. Similarly, none of the compounds are skin sensitive (dermal toxic) or bacterial mutagenic potential drugs using the AMES toxicity examination. However, all the compounds showed high level of toxicity to *Tetrahymena pyriformis* toxicity test. Acute and chronic toxicity were also carried out on the tested compound to determine the safety of the compounds when administered. Exposure to low-moderate doses/concentrations of xenobiotics over long period of time is of significant concern in many treatment strategies or interventions. Chronic studies are designed to identify the lowest dose of a compound that can result in adverse effects (LOAEL), and the highest dose at which no adverse effects are observed (NOAEL). None of the compounds is an inhibitor to hERG I but kolaflavanone and remdesivir may be inhibitors to hERG II. Inhibition of the hERG potassium channel could result in delayed ventricular repolarisation leading to a severe disturbance in the normal cardiac rhythm and disrupt hepatic functions [23].

Conclusion

This study screened apigenin, fisetin, kolaflavanone, and remdesivir as potential molecules that could mitigate/inhibit SARS-COV2 using *in silico* methodology and guide in the development of effective therapeutics to combat COVID-19. Kolaflavanone was observed to exhibit the highest binding affinity with the SARS-COV2 major protease (6LU7). All the three tested phytochemicals (apigenin, fisetin, kolaflavanone) showed more binding affinity with 6LU7 than remdesivir, an established antiviral drug. Binding of these phytochemicals to SARS-COV2 could inhibit or interfere the pathogenesis of COVID-19 thereby preventing its cellular entry and proliferation. The pharmacodynamics and pharmacokinetics properties of the phytochemicals showed that they would be good drug candidates and the toxicological evaluations showed that these phytochemicals have relatively low or no toxic effect in human. However, further experimental and clinical studies are needed to further explore their activities and validate their efficacies against COVID-19.

Declarations

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval

Not Applicable

Consent to participate

Not Applicable

Consent for publication

Not Applicable

Data availability

All data generated or analyzed during this study are included in this published article.

Authors contribution

Conceptualization: OJO; Investigation OJO, OMO, OTO, OBD, BJO, ATO; Project administration: OJO, ATO; Resources; OJO, OMO, OTO, OBD, BJO, ATO; Supervision; OJO, OMO; Roles/Writing - original draft: OJO, OMO, OTO, OBD, BJO, ATO.

References

1. WHO Covid-19 briefing- 6th May 2020. https://who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-breifing-on-covid-19–6-may-2020.
2. Coronavirus COVID-19. https://covid19.ncdc.gov.ng (Accessed May 19, 2020.)
3. Chan JF, To KK, Tse H, Jin DY, Yuen KY (2013) Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol 21:544–55.
4. Huang C, Wang Y, Li X, (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395: 497–506.

5. Li G, Clercq E (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat. Rev. Drug Discov. 19: 1449–14150. https://doi.org/10.1038/d41573-020-00016-0.
6. Liu DX, Fung TS, Chong KKL, Shukla A, Hilgenfeld R (2014) Accessory proteins of SARS-CoV and other coronaviruses. Antivir. Res. 109: 97–109. https://doi.org/10.1016/j.antiviral.2014.06.013.
7. Trott O, Olson AJ (2010) AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry 31(2): 455–461. https://doi.org/10.1002/jcc.21334
8. Lopez-Blanco JR, Aliaga JI, Quintana-Ort, ES, Chacon P (2014) iMODS: Internal coordinates normal mode analysis server. Nucleic Acids Research, 42(Web Server issue), W271–276. https://doi.org/10.1093/nar/gku339
9. Farombi EO, Awogbindin IO, Farombi TH, Oladele JO, Izomoh ER, Aladelokun OB, Ezekiel IO, Adebambo OI, Abah VO (2019) Neuroprotective role of kolaviron in striatal redo-inflammation associated with rotenone model of Parkinson's disease. Neurotoxicology 73:132–141. https://doi.org/10.1016/j.neuro.2019.03.005
10. Uko OJ, Usman A, Ataja AM (2001) Some biological activities of Garcinia kola in growing rats Vet. Arhiv 71 (5): 287-297.
11. Farombi EO, Akanni OO, Emerole GO (2008) Antioxidant and scavenging activities of flavonoid extract (Kolaviron) of *Garcinia kola* Pharmaceutical Biology 40(2): 107-116.
12. Maˇnourová A, Leuner O, Tchoundjeu Z, Van Damme P, Verner V, Pˇribyl O, Lojka B (2019) Medicinal potential, utilization and domestication status of bitter kola (*Garcinia kola* Heckel) in West and Central Africa. Forests 10(124): 1 -18.
13. Awogbindin IO,Olaleye DO, Farombi EO (2015) Kolaviron Improves Morbidity and Suppresses Mortality by Mitigating Oxido-Inflammation in BALB/c Mice Infected with Influenza Virus. Viral Immunology 28: 367–377. 1089/vim.2015.0013
14. Salehi B, Venditti A, Sharifi-Rad M, Kr egiel D, Sharifi-Rad J, Durazzo A, Lucarini M, Santini A, Souto EB, Novellino E, Antolak H, Azzini E, Setzer WN, Martins (2019) The Therapeutic Potential of Apigenin. J. Mol. Sci. 20: 1305. 1-26.
15. Yousefzadeh MJ, Zhu Y, McGowan SJ (2018) Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine 36:18-28.
16. Kashyap D, Sharma A, Sak K, Tuli HS, Buttar HS, Bishayee A (2017) Fisetin: A bioactive phytochemical with potential for cancer prevention and pharmacotherapy. Life Sciences doi:10.1016/j.lfs.2017.12.005
17. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 23(1–3), 3–25. 1997, https://doi.org/10.1016/S0169-409X(96)00423-1
18. Hughes JD, Blagg J, Price DA, Bailey S, Decrescenzo GA, Devraj RV, Ellsworth E, Fobian YM, Gibbs ME, Gilles RW, Greene N, Huang E, Krieger-Burke T, Loesel J, Wager T, Whiteley L, Zhang Y (2008)

Physiochemical drug properties associated with in vivo toxicological outcomes. Bioorganic & Medicinal Chemistry Letters 18(17): 4872–4875. https://doi.org/10.1016/j.bmcl07.071

19. Adeoye AO, Oso BJ, Olaoye IF, Tijjanic H, Adebayo AI (2020) Repurposing of chloroquine and some clinically approved antiviral drugs as effective therapeutics to prevent cellular entry and replication of coronavirus. Journal of biomolecular structure and dynamics. https://doi.org/10.1080/07391102.2020.1765876
20. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, Lee PW, Tang Y (2012) admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. Journal of Chemical Information and Modeling, 52(11), 3099–3105. https://doi.org/10.1021/acs.jcim.9b00969
21. Yazdanian, M, Glynn SL, Wright JL, Hawi A (1998) Correlating partitioning and caco-2 cell permeability of structurally diverse small molecular weight compounds. Pharmaceutical Research, 15(9), 1490–1494. https://doi.org/10.1023/A:1011930411574
22. Srivalli KM, Lakshmi PK (2012) Overview of P-glycoprotein inhibitors: A rational outlook. Brazilian Journal of Pharmaceutical Sciences, 48(3), 353–367. https://doi.org/10.1590/S1984-82502012000300002
23. Oso BJ, Oyewo EB, Oladiji AT (2019) Influence of ethanolic extracts of dried fruit of Xylopiaaethiopica (Dunal) A. Rich on haematological and biochemical parameters in healthy Wistar rats. Clinical Phytoscience, 5(1), 9. https://doi.org/10.1186/s40816-019-0104-4

Tables

Table 1: Molecular docking analysis of the tested compounds against COVID-19 major protease (6LU7)

Compound	Binding energies (kcal/mol)	ligand-amino acid interactions
Apigenin	-6.7	LEU286, LEU287
Fisetin	-7.0	ARG131, THR199, LEU286, LEU287
Kolaflavanone	-7.2	ASN238, TYR237, LEU286, LEU287
Remdesivir	-6.6	ARG131, THR199, LYS137, ASP289, LEU272, LEU287, MET276

Table 2: Molecular properties of the phytochemicals

Descriptor	Apigenin	Fisetin	Kolaflavanone	Remdesivir
Molecular weight	270.24	286.239	588.521	602.585
Lipophilicity (Log P)	2.5768	2.2824	3.7063	2.31218
Number of rotatable bonds	1	1	4	13
Number of acceptors	5	6	12	13
Number of donors	3	4	7	4
Surface area	112.519	117.313	242.369	242.488

Table 3: Predicted absorption properties of the phytochemicals

Model name	Apigenin	Fisetin	Kolaflavanone	Remdesivir
Water solubility (log mol/L)	-3.329	-3.181	-2.9	-3.07
Caco2 permeability (log Papp in 10^{-6} cm/s)	1.007	0.058	0.28	0.635
Intestinal absorption (% Absorbed)	93.25	83.752	76.444	71.109
Skin permeability (log Kp)	-2.735	-2.735	-2.735	-2.735
P-glycoprotein substrate	Yes	Yes	Yes	Yes
P-glycoprotein I inhibitor	No	No	Yes	Yes
P-glycoprotein II inhibitor	No	No	Yes	No

Caco2: Human colon adenocarcinoma-2

Table 4: Predicted *in vivo* distribution of the phytochemicals

Model name	Apigenin	Fisetin	Kolaflavanone	Remdesivir
VDss (human) (log L/kg)	0.822	0.718	-0.634	0.307
Fraction unbound (human) (Fu)	0.147	0.166	0.17	0.005
BBB permeability (log BB)	-0.734	-1.039	-1.259	-2.056
CNS permeability (log PS)	-2.061	-2.282	-3.714	-4.675

VDss: Steady-state volume of distribution, BBB: Blood-brain barrier, CNS: Central nervous system.

Table 5: Predicted human cytochrome P450 promiscuity of the phytochemicals

Model name	Apigenin	Fisetin	Kolaflavanone	Remdesivir
CYP2D6 substrate	No	No	No	No
CYP3A4 substrate	No	No	No	Yes
CYP1A2 inhibitor	yes	yes	No	No
CYP2C19 inhibitor	Yes	No	No	No
CYP2C9 inhibitor	No	Yes	No	No
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	No	No	No	No

Table 6: Predicted *in vivo* clearance of the phytochemicals

Model name	Apigenin	Fisetin	Kolaflavanone	Remdesivir
Total clearance (log ml/min/kg)	0.566	0.421	-0.359	0.198
Renal OCT2 substrate	No	No	Yes	No

OCT2: Organic cation transporter 2.

Table 7: Predicted toxicological profile of the phytochemicals

Model name	Apigenin	Fisetin	Kolaflavanone	Remdesivir
AMES toxicity	No	No	No	No
Max. Tolerated dose (human) (log mg/kg/day)	0.328	0.579	0.442	0.15
hERG I inhibitor	No	No	No	No
hERG II inhibitor	No	No	Yes	Yes
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.45	2.465	2.5	2.043
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	2.298	1.921	3.816	1.639
Hepatoxicity	No	No	No	Yes
Skin sensitization	No	No	No	No
T. pyriformis toxicity (log ug/L)	0.38	0.376	0.285	0.285
Minnow toxicity (log mM)	2.432	2.273	4.004	0.291

AMES: Salmonella typhimurium reverse mutation assay, Max.: Maximum hERG: Human ether-a-go-go-related gene.

Figures

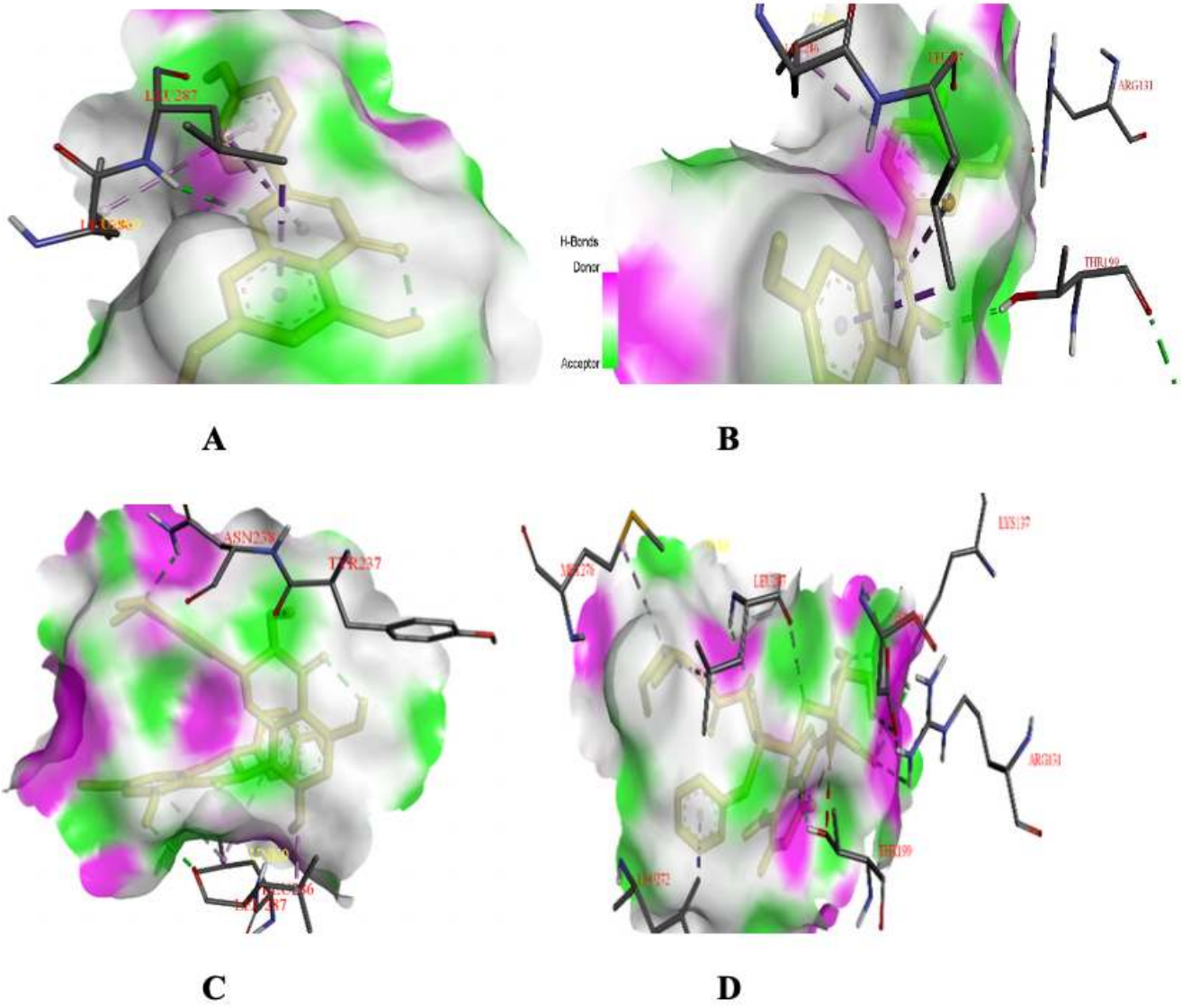

Figure 1

Docking analysis and visualization of 6LU7 binding with (A) Apigenin, (B) Fisetin, (C) Kolaflavanone, (D) Remdesivir