Original Research Article

Molecular Docking, Drug-Likeness and ADMET Analysis of Potential Inhibitors (Ligands) from *Carica papaya* Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Muhammad Y[1*], Shehu Z[2], Iliya S[3], Muhd BK[4], Kani YA[5], Ahmad MB[6], Wali U[7], MH Yeldu[7], Tahiru A[1], Mohammed Y[1], Ahmed AY[7], Yakubu A[8], Habeeb A[9], Fatima IB[2], Saeed SA[10] and Abubakar UF[11]

[1]Department of Chemical pathology, Rasheed Shekoni Specialist Hospital Dutse
[2]Department of Science Laboratory Technology, Jigawa State Polytechnic
[3]Department of Biological Sciences, School of Pure and Applied Sciences, Mount Kenya University Thika, Kenya
[4]Department of Biotechnology Federal University Dutse PMB 7156
[5]College of Medicine and Health Sciences, Federal University Dutse
[6]Department of Chemical Pathology, Faculty of Medical Laboratory Science, Bayero University Kano
[7]Department of Chemical Pathology Faculty of Medical Laboratory Science, Usmanu Danfodiyo University Sokoto
[8,9]Department of Hematology and Blood Group Serology, Rasheed Shekoni Specialist Hospital Dutse
[10]Department of Hematology 44 Reference Hospital Kaduna, Sokoto Road, Badiko, Kaduna-Nigeria
[11]Public Health and Diagnostic Institute, Yusuf Maitama Sule University Kano, Nigeria

Abstract

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease (Covid-19) pandemic has made it a universal health difficulty in both developed and developing countries, spreading fears, uncertainties and death. Worldwide, the disease is skyrocketing, spinning from a total of 124, 719 cases in 118 countries on March 12, 2020 to a high of 1,004,336 cases in 204 countries on April 2, 2020. Out of the 1,004,336 confirmed cases, 704,570 (95%) are categorized as mild cases 37,710 (5%) serious cases 51,556 deaths while 210,500 have recovered. SARS-CoV-2 belongs to beta coronavirus; usually these viruses form a polypeptide after genome transcription that needs to be cleaved enzymatically in order to produce non-structural proteins, this process is only possible with synergistic functions of Main protease or 3-chymotrypsin-like protease (3CLpro) and Papain-like protease (PLpro). Inhibiting these proteases will in no doubt interfere with replication and subsequent release of viral progenies. The current *in silico* study was performed to predict the possibility of 7 phytochemicals from *Carica papaya* as potential inhibitors of Covid-19 proteases and RNA dependent RNA polymerase. The protein structures and ligands were downloaded from RCSB Protein data bank (pdb) and PubChem respectively. The qualitative assessment of physicochemical properties, liphopilicity, water solubility, medicinal chemistry, drug likeness and ADMET were predicted virtually using swissadme. Molecular docking analysis showed that kaempferol, quercetin have good binding affinity and hydrophobic interactions with both Covid-19 proteases and RdRp. However, this hypothesis would be used as a background which needs to be proven otherwise *in vitro*.
Keywords: SARS-CoV-2, Covid-19, Main protease, Papain-like protease, RNA dependent RNA polymerase, *Carica papaya,* Molecular docking, Drug-likeness, *ADMET*.

INTRODUCTION

The emergence of a new corona virus disease in 2019 has made it a universal health difficulty in both developed and developing countries. It was on 31 December 2019, the Wuhan Municipal Health Commission announced cases of viral infections of unknown origin, in Wuhan, Hubei province of China [1]. World health organization (WHO) temporarily named the pathogen as new novel coronavirus (2019-nCoV) on February 11, 2020 [2]. Few weeks later, 2019-nCoV was permanently named as severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) by the International Committee on Virus Taxonomy [1, 3] because of almost 90% genetic resemblance with SARS-CoV. However, some experts in china tried to strike balance between the two nomenclatures where they referred to the disease as human coronavirus 2019 (HCoV-19). SARS-CoV-2 belongs to *Betacoronavirus* and was responsible for the pneumonia outbreaks in Wuhan, a disease later referred to as Covid-19 [2]. On March 11, 2020, WHO declared global pandemic of

Covid-19 [2]. Since then, China and many other countries in Europe and Asia have experienced rapidly increasing trend of the disease, while African countries have begun to record incidences. Globally, the disease is currently skyrocketing, spinning from a total of 124, 719 cases in 118 countries on March 12, 2020 to a high of 1,004,336 cases in 204 countries on April 2, 2020 (John Hopkins and WHO worldo meters, 2020). Out of the 1,004,336 confirmed cases, 704,570 (95%) are categorized as mild cases 37,710 (5%) serious cases 51,556 deaths while 210,500 have recovered) [3].
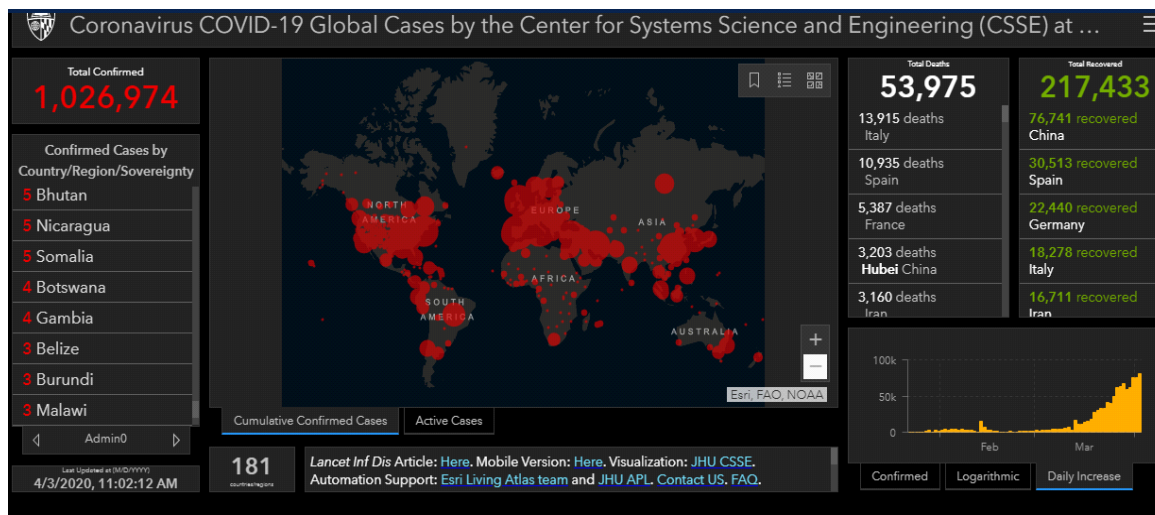

Fig-1: Screenshot of John Hopkins worldo meters as at 2nd April, 2020.

Pillaiyer, *et al* [4] states, there is no effective treatment for SARS-CoV in spite of the researches that have been undertaken for almost 17 years now. In relation to SARS-CoV-2, similarly no drug or vaccine has yet been approved, despite the world growing concerns, intense efforts and dedication being made by many researchers and top authorities towards addressing the menace of the newly emerged COVID-19 [2]. Use of herbal products for therapeutic purposes (phytomedicine) has played a great role in the management of many maladies since time immemorial.

These plant products contain active biological compounds (phytochemicals) that prevent or treat disease condition [5, 6]. More than 70% of developing countries use plant based materials as sources of developing new drug rather than synthetic chemicals [7]. *Carica papaya* (pawpaw) belonging to the family Caricaceae, has been reported to have antiviral activities due to presence of some phytochemicals such as kaempferol, quercetin, Chloregenic acid etc. [8]. The findings of the present study will provide other researchers with opportunities to identify the right drug to combat COVID-19.

Protein Targets

Main protease or 3-chymotrypsin-like protease (3CLpro): SARS-CoV-2 belongs to beta coronavirus; usually these viruses form a polypeptide after genome transcription that needs to be cleaved enzymatically in order to produce various non-structural proteins (nsps) [9]. 3CLpro executes its functions by cleaving polyprotein at 11 distinct sites which later assemble to form replicase-transcriptase complex (RTC). Thus, 3CLpro protease is essential and critical in the viral replication and therefore may serve as a potential target for anti-SARS-CoV-2 inhibitors.

Papain-like protease (PLpro): Proteolytic cleavage for generation of various nsps by 3CLpro is mediated by PLpro. This protease cleaves the nsp1/2, nsp2/3 and nsp3/4 boundaries. The structure of PLpro was built based on 4OW0, the PLpro structure of SARS-COV.

RNA dependent RNA polymerase (RdRp/Nsp12): This is a polymerase which binds to its essential cofactors, nsp7 and nsp8. It is equally important in replication and transcription of the SARS-CoV 2 genome. The structure of RdRp was built based on the RdRp structure of SARS-CoV [10, 11].

Fig-2: Cartoon structural forms of (A) Main protease, (B) Papain-like protease and (C) RNA dependent RNA Polymerase of Covid-19.
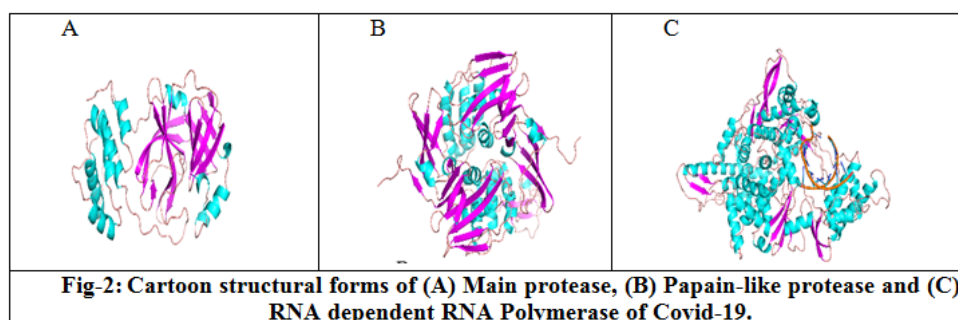
EXPERIMENTAL WORK

Preparation and Optimization of Protein and Ligand Structures

Three (3) structures of covid-19 proteins namely; main protease (3CL^{Pro}), Papain-like protease PL^{pro} and RNA dependent RNA polymerase (RdRp) with PDB codes of 6LU7, 6W9C and 6M71 respectively were retrieved from protein data bank (www.rcsb.org/pdb). Similarly, seven (7) active compounds (phytochemicals) extracted from *Carica papaya* i.e. Quercetin, Chlorogenic acid, 5,7-dimethoxycoumarin, Caffeic acid, Kaempferol, p-Coumaric acid and Protocatechuic acid were downloaded from PubChem and saved in sdf format. Finally, Nelfinavir, lopinavir and remdesivir structures in sdf were also downloaded and used as reference drugs; these drugs were recommended in the treatment of SARS and MERS and as such used as controls. Optimization of proteins and ligands was performed using MGL Tools and Avogadro version 1.2, with Force Field type MMFF94 respectively. The proteins optimization was achieved by removal of water, other atoms and subsequent addition of polar hydrogen. PyRx software was used to convert the ligand files into pdbqt format with Gasteiger charge added. The box center for docking was defined according to the information of active sites or binding sites of its homologs of SARS-COV.

Receptor-Ligand Docking using PyRX, Pymol and Biovia Discovery Studio virtual screening software

PyRx software was used for performing virtual screening. PyRx package comprises of AutoDock Vina, Mayavi, Open Babel, etc. For a successful docking analysis, viral proteins and ligands were converted to pdbqt files from pdb format. Pymol and Biovia Discovery Studio were also used in the docking process. The interacting amino acid residues in the active sites were identified using Biovia Discovery Studio.

Computation of physicochemical properties, Pharmacokinetics, Medicinal chemistry, Drug likeness and ADMET

The parameters were virtually predicted using swissADME web tool (www.swissadme.ch) [12]. It is a freely accessible server developed and maintained by Swiss Institute of Bioinformatics (SIB) to compute and evaluate predictors for drug discovery. The structures of the ligands were designed and placed on the server then automatically converted to SMILES format.

Table-1.0: Properties of SARS-Cov2 (Covid-19) Potential Inhibitors from *Carica papaya* and drugs of reference against SARS

PubChem CID	Compounds name	2D Structure	MF	MW(g/mol)
64143	Nelfinavir		$C_{32}H_{45}N_3O_4S$	567.8
92727	Lopinavir		$C_{37}H_{48}N_4O_5$	628.8
121304016	Remdesivir		$C_{27}H_{35}N_6O_8P$	602.6
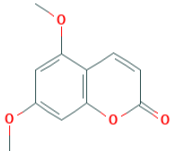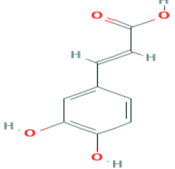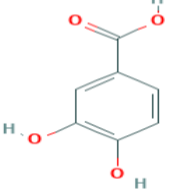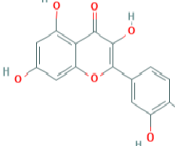
2775	5,7-dimethoxycoumarin		$C_{11}H10O4$	206.19
689043	Caffeic acid		C_9H8O4	180.16
1794427	Chlorogenic acid		$C_{16}H18O9$	354.31
5280863	Kaempferol		$C_{15}H10O6$	286.24

Table-2.0: Physicochemical Properties of ligands

Ligands	MW(g/mol)	HA	AHA	FCsp3	RB	HBA	HBD	MR	TPSA(Å²)
Quercetin	302.24	22	16	0.00	1	7	5	78.04	131.36
Chloregenic acid	354.31	25	6	0.38	5	9	6*	83.50	1.64.75
5,7-dimethoxycoumarin	206.19	15	10	0.18	2	4	0	55.47	58.67
Caffeic acid	180.16	13	6	0	2	4	3	47.16	77.76
Kaempferol	286.24	21	16	0	1	6	4	76.01	111.13
p-Coumaric acid	164.16	12	6	0	2	3	2	45.13	57.53
Protocatechuic acid	154.12	11	6	0	1	4	3	37.45	77.76

KEY *values that exceeded the limits established by the rule.
MW=Molecular weight; ClogP=Calculated logarithm of partition coefficient between n-octanal and water; HBA=Hydrogen bond acceptors; HBD=Hydrogen bond donors.

Table-3: Liphopilicity of the Ligands

Ligands	LogP$_{o/w}$(iL OG)	LogP$_{o/w}$(XL OGP)	LogP$_{o/w}$(WL OGP)	LogP$_{o/w}$(ML OGP)	LogP$_{o/w}$(SILI COST-IT)	Consensus logP$_{o/w}$
5,7-dimethoxycoumarin	2.45	1.85	1.81	1.05	2.42	1.92
Caffeic acid	0.97	1.15	1.09	0.70	0.75	0.93
Chloregenic acid	0.87	-0.42	-0.75	-1.05	-0.61	-0.39
Kaempferol	1.70	1.90	2.28	-0.03	2.03	1.58
p-Coumaric acid	0.95	1.46	1.38	1.28	1.22	1.26
Protocatechuic acid	0.66	1.15	0.80	0.40	0.26	0.65
Quercetin	1.63	1.54	1.99	-0.56	1.54	1.23

Table-4.0: Water solubility assessment of the ligands

Parameter	5,7-dimethoxycoumarin	Caffeic acid	Chloregenic acid	Kaempferol	p-Coumaric acid	Protocatechuic acid	Quercetin
Log S (ESOL)	-2.65	-1.89	-1.62	-3.31	-2.02	-1.86	-3.16
Solubility (mg/ml)	4.67e-01	2.32e+00	8.50e+00	1.40e-01	1.58e+00	2.14e+00	2.11e-01
Class	Soluble	Very soluble	Very soluble	soluble	Soluble	Very soluble	Soluble
Log S (Ali)	-2.49	-2.38	-2.58	-3.86	-2.27	-2.38	-3.91
Solubility	6.63e-01	7.55e-o1	9.42e-01	3.98e-02	8.73e-01	6.45e-01	3.74e-02
Class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Log S (SILICOS-IT)	-3.87	-0.71	0.40	-3.82	-1.28	-0.60	-3.24
Solubility	2.76e-02	3.51e+01	8.94e+02	4.29e-02	8.67e+00	3.83e+01	1.73e-01
Class	soluble	soluble	soluble	soluble	Soluble	Soluble	Soluble

Table-5.0: Drug likeness properties of the Ligands

	Lipinski's rule of five	Ghose	Veber	Egan	B-Score
	MW<500Da	160≤MW≤480	RB≤10	WLOGP≤5.88	
	LogP<5	-0.4≤WLOGP ≤5.6	TPSA≤140	TPSA≤131.6	
	HBD 5	40≤MR≤130			
	HBA<10	20≤atoms≤70			
5,7-dimethoxycoumarin	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0.55
Caffeic acid	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0.56
Chloregenic acid	Yes; 1 violation	Yes; 1 violation	Yes; 1 violation	Yes; 1 violation	0.11
Kaempferol	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0.55
p-Coumaric acid	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0.56
Protocatechuic acid	Yes; 0 violation	No; 3 violation	Yes; 0 violation	Yes; 0 violation	0.56
Quercetin	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0.55

KEY

MW=Molecular weight; HBA=Hydrogen bond acceptors; HBD=Hydrogen bond donors; B-score=Bioavailability score; MR= Molar refractivity; TPSA= Topological polar surface area.

Table-6.0: Medicinal chemistry assessment of the ligands

Parameters	PAINS	Brenk	Leadlikeness	Synthetic accessibility
				From 1 (very easy) to 10 (verydifficult)
5,7-dimethoxycoumarin	0 alert	1 alert: cumarine	No; 1 violation:MW<250	2.78
Caffeic acid	1 alert:catecholA	2alerts:catechol_A, Michael acceptor1	No; 1 violation; MW<250	1.81
Chloregenic acid	1 alert:catechol_A	2 alert:catechol, michael acceptor1	No; 1 violation:MW<250	4.16
Kaempferol	0 alert	0 alert	Yes	3.14
p-Coumaric acid	0 alert	1 alert: michael acceptor_1	No; 1 violation; MW<250	1.61
Protocatechuic acid	1alert:catechol_A	1alert:catechol_A	No; 1 violation; MW<250	1.07
Quercetin	1 alert:catechol_A	1 alert:catechol	Yes	3.23

PAINS= Pan Assay interference structures

Table-7.0: Predicted *ADMET* profile of the ligands Absorption

Parameter	5,7-dimethoxycoumarin	Caffeic acid	Chloregenic acid	Kaempferol	p-coumaric acid	Protocatechuic acid	Quercetin
GIA	+++	+++	+	+++	+++	+++	+++
BBB	+	+	+	+	+	+	+
P-gp substrate	No	No	No	No	No	No	No
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI
LogKp(Skin permeation)(cm/s)	-6.24	-6.58	-8.76	-6.70	-6.26	-6.24	-7.05
Metabolism							
CYP1A2 inhibitor	NI	NI	NI	Yes	NI	NI	Yes
CYP 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI
CYP 2C9 inhibitor	NI	NI	NI	NI	NI	NI	NI
CYP 2D6 inhibitor	NI	NI	NI	Yes	NI	NI	Yes
CYP 3A4 inhibitor	NI	NI	NI	NI	NI	Yes	Yes
CYP 2C9 Substerate	NI	NI	NI	NI	NI	NI	No
CYP 2D6 substrate	NI	NI	NI	NI	NI	NI	NI
CYP 3A4 substrate	NS	NS	NS	NS	NS	NS	NS
Toxicity							
	NT	NT	NT	NT	NT	NT	NT

GIA= Gastrointestinal absorption; BBB= Blood brain barrier permeant; Pgp= P-glycoprotein substerate; CYP= Cytochrome P450; NI= Non-inhibitor; NS= Non-substerate.
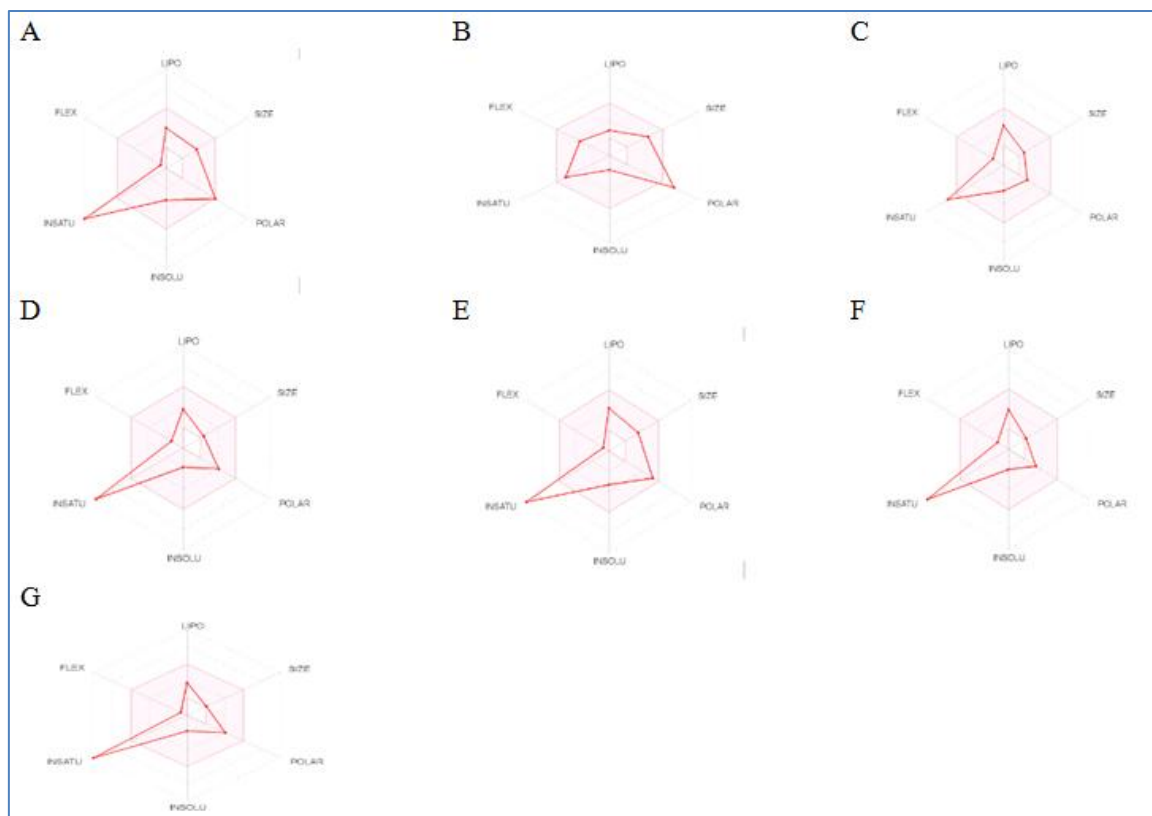
Fig-3: Bioavailability radar of Potential inhibitors (A) Quercetin; (B) Chloregenic acid; (C) 5,7 dimethoxy coumarin; (D) Caffeic acid; (E) Kaempferol;(F) p-Coumaric acid and (G) Protocatechuic acid

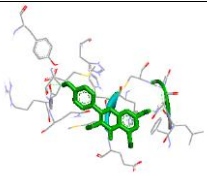**Table-8.0: Molecular docking analysis of Potential inhibitors against Main Protease of Covid-19**
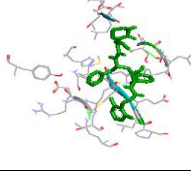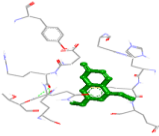
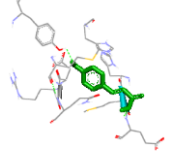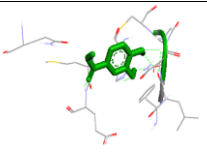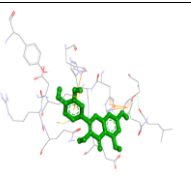| Ligands	Binding energy (Kcal/mol)	Hydrophobic interactions	Residues interacting with Ligand through H-Bonding and other interaction
Nelfinavir	-7.9		Leu27,Met49,Try54,His41,Asn142, Gly143,Cys145,His164,His165,Glu 166,Leu167,Pro168,Asp187,Arg188 ,Gln189,Thr190
Lopinavir	-8.3		Thr24,Thr25,Thr26,Leu27,His41,M et49,Tyr54,Gly143,Ser144,Asn142,, Leu141,Phe140,His164,Met165,Glu 166,Glu167,PPro168,Asp187,Arg18 8,Gln189,Thr190,Thr192
5,7-dimethoxycoumarin	-5.70		Tyr54, His41, His164, Asp 187, Arg 188, Met 165,Gln189, Met 165, Thr 190, Glu166, Glu166
Caffeic acid	-5.80		Phe140,Leu141,Asn142,Gly143,Ser 144,Cys145,His163,Glu166,Met165 ,Gln189
Chlorogenic acid	-7.40		Gly143, Ser144, Asn142, Cys145, Leu141, Hi164, Met165,Glu166, Leu167,Gln189,Pro168,Thr190,Ala 191 Gln192,
Kaempferol	-7.80		Tyr54,His41,Met49,Gly143,Cys145 ,Ser144,Asn142Leu141,Phe140,His 163,His164,Met165,Glu166,Asp187 ,Arg188,Gln189
p-Coumaric acid	-5.10		Try54,His41,MMet49,His164,As187 ,Met165,Glu166, Arg188,Arg189
Protocatechuic acid	-5.40		Phe140, Leu141,Asn142, Gly143, Ser144, Cys145,His163, Met165,Glu166, Gln189
Quercetin	-7.9		Try54,His41,Ser144,His163,His164 , Leu141,Phe140,Asp187,Met49,Met 165,Met49, Glu166, Gln180

Table-9.0: Molecular docking analysis of Potential inhibitors against Papain-like Protease of Covid-19
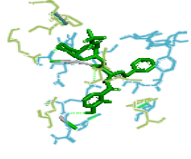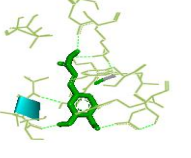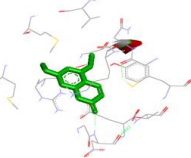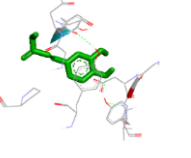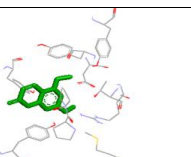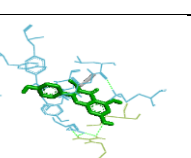
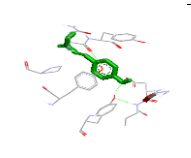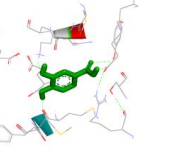| Ligands	Binding energy (Kcal/mol)	Hydrophobic interactions	Residues interacting with Ligand through H-Bonding and other interaction
Nelfinavir	-9.9		Asn109,Cys155,Asn156,Lys157,Gly160,Glu161,Leu162,Gly163,Asp164glu167,Tyr264,Tyr268,Gln269
Lopinavir	-5.7		Tyr456,Tyr540,Thr556,Val557,Ala558, Asp623, Arg624, Glu665, Lys676,Thr680,Ser681, Ser682
5,7-dimethoxycoumarin	-6.8		Cys155,Asn156,Lys157,Gly163,Asp164,Arg166,Glu167,Thr168,Ser170,Tyr171,Val202,Met206,Met208.
Caffeic acid	-6.6		Gly163,Asp164,Val165,Pro248,Tyr264,Gly266,Asn267,Tyr268.
Chlorogenic acid	-6.8		Asp164,Arg166,Met208,Pro247,Pro248,Tyr264,Tyr268,Tyr268,Tyr273,Thr301
Kaempferol	-8.3		Lys157,Leu162,Leu163,Glu,Asp164,Arg166,Glu167,Met208,Tyr264,Tyr268,Gln269,Tyr273
p-Coumaric acid	-6.5		Gly163,Asp164,Val165,Pro248,Tyr264,Tyr273,Asn267,Tyr268.
Protocatechuic acid	-6.6		Cys155,Asn156,Lys157,Glu161,Arg166,Glu167,Ser170,Try171,Glu203,Met206,Tyr207,Met208
Quercetin	-6.8		Lys155,Asn156,Lys157,Glu161,Leu162,Arg166,Glu167,Ser170,Tyr171,Glu203,Met206,Tyr207,Met208,

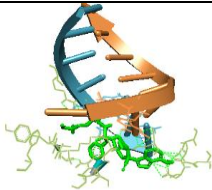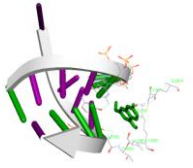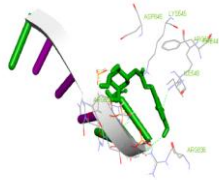**Table-10: Molecular docking analysis of Potential inhibitors against RNA dependent RNA polymerase of Covid-19**
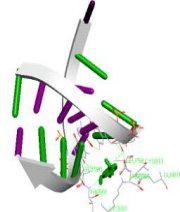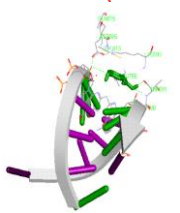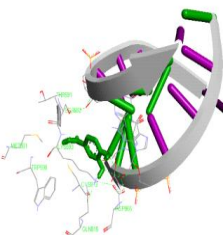
Ligands	Binding energy (Kcal/mol)	Hydrophobic interactions	Residues interacting with Ligand through H-Bonding and other interaction
Remdesivir	-9.6		Phe441,Ly545,Tyr546,Ile548,Arg555,Thr556,Val557,Ser682,Thr687,Asn691,Ser759,760,Arg858
5,7-dimethoxycoumarin	-7.6		Gln815,cys813,leu758,lys593,val588,gly590,thr591,
Caffeic acid	-7.5		Ile589,Gly590,Thr591,Ser592,Lys593,Ileu758,Cys813,Gln815,Asp865
Chlorogenic acid	-8.7		Lys545,Asp845,Arg555,Phe441,Ile548,Arg836,Arg858
Kaempferol	-8.4		Gln815,Asp865,Cys813,Lys593,Leu758,Gly590,Thr591
p-Coumaric acid	-6.8		Leu758,Cys813lys593,Thr591,,Gly590,Asp865,Gln815
Protocatechuic acid	-7.0		Gln815,Asp865,Cys813,Trp598,Lys593thr591,Ser592met601
Quercetin	-9.0		Arg553,Asp452,Arg555,Arg624,Asp623,Thr680,Asp760,Asn691,Ser687,Thr687,Thr556,Ser682

Table-11: Summary of top ligands binding energy interacting with Covid-19 proteases and RdRp

Parameters	Nelfinavir	Lopinavir	Remdesivir	5,7-dimethoxycoumarin	Caffeic acid	Chloregenic acid	Kaempferol	p-Coumaric acid	Protocatechuic acid	Quercetin
3Clpro	-7.9	-8.3	-	-5.7	-5.8	7.4	-7.8	-5.1	-5.4	-7.9
Plpro	-9.9	-5.7	-	-6.8	-6.6	-6.8	-8.3	-6.6	-6.6	-6.8
RdRp	-	-	-9.6	-7.6	-7.5	-8.7	-8.4	-6.8	-7.0	-8.7

DISCUSSION

Researchers around the globe are exploiting every avenue in finding cure for the ravaging Covid-19 by evaluating existing antiviral agents, screening of chemical compounds with antiviral potentials and redevelopment of drugs based on understanding coronavirus genome. The qualitative assessment of physicochemical properties, liphophilicity, water solubility, medicinal chemistry, drug likeness and absorption, deposition, metabolism, excretion, toxicity (i.e. ADMET), profile of the ligands shown in table 2, 3, 4, 5, 6 and 7 respectively were predicted virtually using swissadme server (www.swissadme.ch) [12]. Torpological polar surface area (TPSA) is an important physico chemical property that predicts oral absorption of a chemical compound, TPSA values greater than $140Å^2$ is indicative of limited cell membrane permeability and values below $140Å^2$ signifies good permeability and oral absorption to which all the ligands in the current study fall within. The liphopilicity of ligands defines the degree of solubility, good permeability across cell membrane and thus good absorption. This molecular property was evaluated accordingly and all the compounds prove to have good permeability because the predicted values of miLogP, iLogP, Log P and MolLogP were below 5. Our findings further revealed that all the ligands possess a drug-like property having completely obeyed Lipinski's rule of five which states that for a compound to be safely used as therapeutic agent it must not violate more than two of the following parameters (MW <500Da, LogP < 5, HBD 5, HBA<10). Other (3) different measures (Ghose, Veber and Egan) satisfactorily approved the drug like nature of all the ligands except Protocatechuic acid with 3 violations in Ghose rule. The amount of active drug reaching blood stream (bioavailability) is an important parameter in drug discovery, our results showed that all the ligands have excellent bioavailability score (only chlorogenic acid with values <0.55. Medicinal chemistry test predicted all the ligands to have very easy synthetic accessibility, in addition, PAINS analysis of structural alert was done to identify functional groups in the ligands with potentials of causing cancers, mutations or interference with metabolism, kaempferol, p-Coumaric acid and 5,7-dimethoxycoumarin revealed zero structural alert, while quercetin, caffeic acid, Chlorogenic acid and protocatechuic acid shown to contain catechol A and this could be used as preliminary alert in developing the drugs. Molecular docking analysis was performed to predict the possibility of 7 phytochemicals from *Carica papaya* as potential inhibitors of Covid-19 proteases and RNA dependent RNA polymerase having satisfied most of the criteria to be used as a therapeutic agent. Results shown in table 8, 9 and 10 represent molecular docking studies of the ligands against 3CLPro, PLpro and RdRp of SARS-COV 2 respectively. The binding affinity is dependent on the type and amount of bonding formed between the proteins (3CLPro, PLpro and RdRp) and the ligands, the lower the binding affinity the better the interactions. The present study revealed the inhibition potential of ligands against 3CLPro, ranked by binding affinity (Kcal/mol) as follows; nelfinavir > quercetin >lopinavir > kaempferol > Chlorogenic acid > caffeic acid > 5,7-dimethoxycoumarin > protocatechuic acid > p-Coumaric acid, quercetin has the same binding affinity as nelfinavir and only 0.1kcalmol^{-1} and 0.5 kcalmol^{-1} ahead of kaempferol and chlorogenic acid respectively. Similarly, the results of docking analysis between PLpro and the ligands surprisingly revealed that all the ligands performed better than lopinavir (-5.7kcalmol^{-1}) and kaempferol is reported to have the highest binding affinity (-8.3 Kcalmol^{-1}) and better interactions compared to the rest of ligands. The binding energies obtained from docking RdRp with remdesivir, 5,7-dimethoxycoumarin, caffeic acid, chlorogenic acid, kaempferol, p-coumaric acid, protocatechuic acid and Quercetin were -9.6, -7.6, -7.5, -8.7, -8.4, -6.8, -7.0 and -9.0 respectively. Therefore, quercetin, chlorogenic acid and kaempferol may have anti-RdRp bioactivities.

CONCLUSION

SARC-COV and MERS were the two coronaviruses known to have caused outbreaks in human before the identification of Covid-19 in China. In the search for therapeutic agents against Covid-19 pandemic, seven (7) ligands from *Carica papaya* were subjected to different test of bioavailability, solubility, liphophilicity, medicinal chemistry and ADMET to

ascertain their drug likeness and potentiality of being used as therapeutic agents. Furthermore, the ligands were accordingly docked with Covid-19 3CLPro, PLpro and RdRp to study the interactions, binding affinity as well as potential inhibition property of the ligands against SARS-COV 2. Molecular docking analysis showed that kaempferol and quercetin possess good binding affinity and hydrophobic interactions with both Covid-19 proteases and RdRp. However, Remdesivir inhibition activity against RdRp was comparable to none of the ligands. Furthermore, these findings could be used as a background which in *vitro* and *in vivo*.

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Conflicts of interest
The authors declare no conflict of interest.

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