Natural compounds from Djiboutian Medicinal plants as inhibitors of COVID-19 by *In silico* investigations

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Abstract:

The new coronavirus type SARS-Cov 2 (severe acute respiratory syndrome), which appeared in autumn 2019 in China, became a global pandemic in a few months. In this work, we looked for the potential anti SARS-Cov 2 of the compounds isolated from three Djiboutian medicinal plants namely *Acacia seyal*, *Cymbopogon commutatus*, and *Indigofera caerulea*. For this we carried out a docking with nine biomolecules, β-Sitosterol , Quercetin, Catechin, Lupeol, Rutin, Kaempferol, Gallic acid, Piperitone and Limonene on three target sites which are SARS-CoV-2 main protease (Mp), SARS-CoV-2 receptor binding domain (RBD) and human furin protease. These targets are chosen because of their role in the process of penetration of the virus into human cells and its multiplication. The phenolic compounds have a very good afinity on these three target sites with binding energies of up to -9.098 kcal/mol for rutin on SARS-CoV-2 Mp, much better than the two reference drugs hydroxychloroquine (-5.816 kcal / mol) and remdesivir (-7.194 kcal/mol). These natural compounds do not present toxicities and can be used pending *In vitro* and *In vivo* evaluations.

Keywords: Bio molecules, Djibouti medicinal plant, anticovid 19 and molecular docking

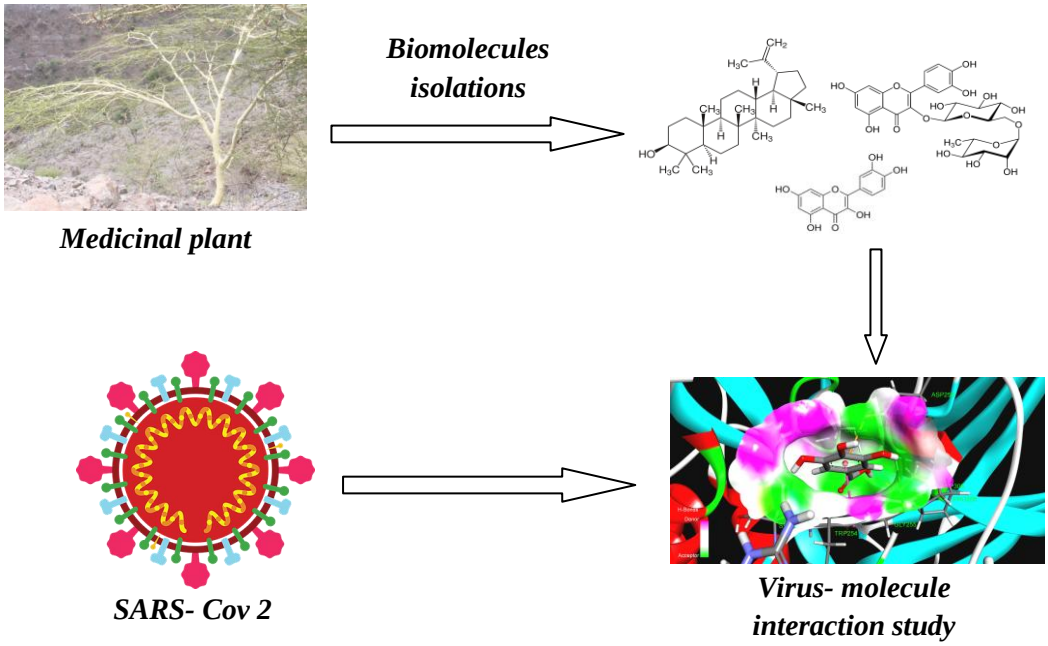
Résumé:

Le nouveau coronavirus type SARS-Cov 2 (severe acute respiratory syndrome) apparu en automne 2019 en chine est devenue une pandémie mondiale en quelques mois. Dans ce travail, nous avons recherché les potentielles anti SARS-Cov 2 des composés isolés à partir de trois plantes médicinales djiboutiennes à savoir *Acacia seyal*, *Cymbopogon commutatus* and *Indigofera caerulea.* Pour cela nous avons effectué un docking avec neuf biomolécules, β-Sitosterol, Quercetine, Catechine, Lupeol, Rutin, Kaempferol, Acide gallique, Piperitone et Limonène sur trois sites cibles de ce virus qui sont SARS-CoV-2 main protease (Mp), SARS-CoV-2 receptor binding domain (RBD) et human furin protease. Ces cibles sont choisies en

raison de leurs rôles dans le processus de pénétration du virus dans les cellules humaines et de son multiplication. Les composés phénoliques ont une très bonne affinité sur ces trois sites cibles avec des énergies de liaison allant jusqu'à -9.098 kcal/mol pour la rutin sur SARS-CoV-2 Mp, bien meilleure que les deux médicaments de référence hydroxychloroquine (-5,816 kcal/mol) et remdesivir (-7,194 kcal/mol). Ces composés naturels ne présentent pas des toxicités et peuvent être utilisés en attente des évaluations *In vitro* et *In vivo*.

Mots clés : Biomolécules, plante médicinale Djiboutienne, anticovid 19 et docking moléculaire.

Graphical abstract



Introduction

Coronaviruses are viral particles and their outer envelope which has spicules, made up of the surface protein S, gives the characteristic crown appearance visible by electron microscopy (Vabret et al. 2009). These viruses affect both humans and animals, and in some cases cause serious infections of the respiratory systems.

The new coronavirus, abbreviated covid 19, appeared in autumn 2019 in China and has since spread to the rest of the world. In the absence of vaccination, treatments are tried to reduce the viral load, and the effects of the induced symptoms. As part of this, a European program

called discovery is testing four molecules against the coronavirus, namely remdesivir, lopinavir, ritonavir, and hydroxychloroquine (INSERM 2020).

Everywhere the search for effective therapeutic molecules is intensifying and, due to the urgency of the situation, evaluations by computer simulation can save time. The interaction between these molecules and specific targets of the coronavirus is measured.

Three targets are favored in the search for effective treatments. They are Furin, a kind of proprotein convertases, and receptor binding domain of SARS-CoV-2 spike protein to prevent viral entry and SARS-CoV-2 main protease essential of viral replication. (Walls et al. 2020; Dhama et al. 2020).

Plants have been very present in the treatment of human pathologies for thousands of years. Medicines or compounds very effective of vegetable origin already exist on International market: the isolated maprouneacin of the *Maprounnea africana* is used like antidiabetic agent, Taxol® (paclitaxel resulting from *Breviflora taxus*) is used like notorious antitumor or artemisinin (*Artemisia annua*) is used as an effective antimalarial agent against all resistant strains of Plasmodium (Ajibesin et al. 2008).

Djibouti, East Africa country, has an arid and desert climate. The average rainfall is low, around 250 mm (Mahmoud et al. 2014). However, more than 800 species are listed and their adaptation under these difficult conditions may be of interest for their medicinal uses.

As part of the promotion of Djiboutian medicinal plants, various bioactive compounds have been isolated for their antimicrobial and anticancer effects. In this present study we will evaluate the potential anticovid therapeutics of these biomolecules through molecular simulation on the targets SARSCoV-2 RBD, SARS-CoV-2 main protease, and human furin protease. We will determine the energies of molecule-target virus interaction, ADME (absorption, distribution, metabolism, and excretion) as well as possible toxicities generated from these molecules.

Materials and methods

1. Study compound

The nine compounds tested are β-Sitosterol, Quercetin, Catechin, Lupeol, Rutin, Kaempferol, Gallic acid, Piperitone, and Limonene (Figure 1). They were isolated from three Djiboutian

medicinal plants: *Acacia seyal*, *Cymbopogon commutatus*, and *Indigofera caerulea* (Picture 1). The extractions and isolations of these compounds are described in our previous publications (Elmi et al. 2018; Elmi 2018; Elmi et al. 2020).

Two drugs against covid are used for comparison: Remdesivir and Hydrochloroquine (Figure 1).

Picture 1 :(A) *Acacia seyal* , DAY, Tadjourah district (North of Djibouti) ; (B) *Cymbopogon commutatus*, BARA, Ali sabieh district (Center of Djibouti) and (C) *Indigofera caerulea*, ABAIDO, Dikhil district (South West of Djibouti)

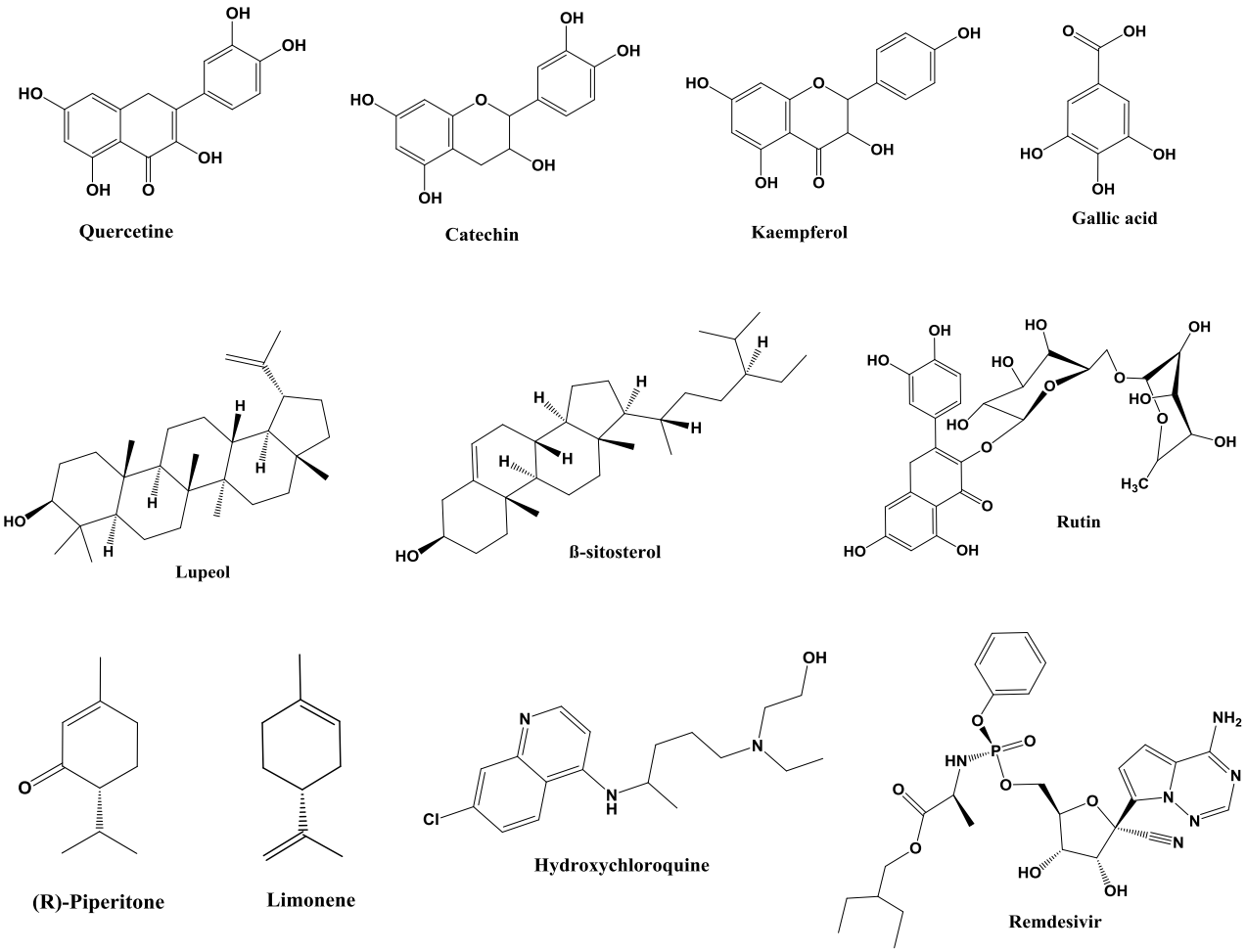


Figure 1: Molecular structure of selected compounds and drug references

2. *In-silico* Investigation

2.1. Proteins and Chemical Compounds Studied In This Investigation

Three proteins were selected for the purpose of this study; 1.SARS-CoV-2 main protease (PDB ID: 5R84) (Fearon et al. 2020), 2.Human furin protease (PDB ID:5MIM) (Dahms, Jiao, et Than 2017), and 3.SARS-CoV-2 receptor-binding domain (PDB ID: 6VW1)(Shang et al. 2020). Nine compounds were also selected; 1.β-Sitosterol (PubChem CID 222284), 2.Quercetin (PubChem CID 5280343), 3.Catechin (PubChem CID 9064), 4.Lupeol (PubChem CID 259846), 5.Rutin (PubChem CID 5280805), 6.Kaempferol (PubChem CID 5280863), 7.Gallic acid (PubChem CID 370), 8.piperitone (PubChem CID 6987), 9.Limonene (PubChem CID 22311), along with two reference drugs remdesivir (PubChem CID 121304016), and hydroxychloroquine (PubChem CID 3652).

2.2. Molecular Docking: Preparation of Ligand

The chemical structures of eleven selected compounds were obtained from PubChem an online repository of chemical compounds (https://pubchem.ncbi.nlm.nih.gov/). The structures were obtained in 2D SDF format. A bioinformatics tool called LigPrep was used to performing ligand preparation. LigPrep is set in Schrödinger suite-Maestro (v 11.1). The following parameters were taken into consideration during this job: the structure was set as project table, the force field was set at OPLS3, the target pH was 7.0 ± 2.0 using Epik and the output format was Maestro.

2.3. Molecular Docking: Preparation of Protein

The desire proteins were taken from Protein Data Bank (PDB) an online database (https://www.rcsb.org/). The three-dimensional protein structures were downloaded in pdb format (Berman et al. 2002). The Resolution was 1.83 Å, 1.9 Å, and 2.68 Å of selected proteins with PDB ID: 5R84, 5MIM, and 5R84 respectively. Preprocessing, optimization, and minimization were done by using the Protein Preparation Wizard for preparing the proteins (Friesner et al. 2004). This wizard is also included in Schrödinger suite-Maestro (v 11.1). The following parameters were used in this job; the structures were optimized at pH 7.0, remove waters with less than 3 H-bond to non-waters, and minimized the proteins using OPLS3 force field. Then generate the receptor grid by using PockDrug an online tool for selecting the best docking site (Borrel et al. 2015).

2.4. Molecular Docking: Glide Molecular Docking

The molecular docking was performed to understand the possible mechanism of the selected compound comparing with two reference drugs against the receptors associate with COVID-19 and human. The docking was completed by using the Ligand Docking tool attaches in Schrödinger suite-Maestro (v 11.1). Then the spreadsheet and 2d interaction figures were collected for further study. Discovery Studio (v 4.1) software was used for more understanding via 3d visualization (Discovery Studio 2008).

2.5. Prediction of the Pharmacokinetic Parameter (ADME)

Several pharmacokinetic properties such as absorption, distribution, metabolism, excretion (ADME) are important to developing a drug. These following properties are investigated by SwissADME an online tool to determine various biochemical properties (http://www.swissadme.ch/) (Daina, Michielin, et Zoete 2017). Some parameters were determined for evaluating the compounds from the SwissADME database based on the Lipinski's and Veber's Rules (Minovski, Perdih, et Solmajer 2012). The following parameters were molecular weight, hydrogen bond acceptor, hydrogen bond donor, logP value, Lipinski's Violations value, number of the rotatable bond (NRB), and topological polar surface area (TPSA).

2.6. Prediction of Toxicological Properties

Toxicological determination is the most prime considerations in case of the development of new drugs. An online bioinformatics tool named AdmetSAR was used to evaluating the toxicological properties of desire compounds (Cheng et al. 2012). The following parameters were counted in this study such as rat acute toxicity, acute oral toxicity, ames toxicity, and carcinogenic properties.

Results and discussion

Molecular docking of nine biomolecules and two reference drugs is carried out at three target sites: SARS-CoV-2 main protease, SARS-CoV-2 receptor binding domain, and human furin protease. Among the different types of interaction between the therapeutic molecule and the targeted active site, the hydrogen bond established with the residues of the active site is critical (Rane et al. 2020). The affinity of this bond is evaluated using binding energy (Kcal / mol). The lower energy corresponds the better affinity between the two entities (target site

and therapeutic molecule).The best target site is SARS-CoV-2 Mp where five compounds (45%) have binding energy (BE) ≤ -7 kcal/mol. The rank of each ligand in terms of the least BE among ligands is also provided as fellowing:

SARS-CoV-2 main protease : rutin > Catechin > kaempferol > **remdesivir** > quercetin > **hydroxychloroquine** > piperitone > gallic acid > limonene> β-Sitosterol > lupeol ;

SARS-CoV-2 receptor binding domain : **remdesivir** > rutin> Kaempferol > Catechin > Quercetin > piperitone > gallic acid > **hydroxychloroquine** > limonene> lupeol > β-Sitosterol ;

human furin protease : quercetin> catechin> rutin >gallic acid> kaempferol> **remdesivir** > **hydroxychloroquine** > piperitone> β-sitosterol> lupeol> limonene.

We note that the five phenolic compounds have a better BE than the terpene compounds whatever the active site (tableau 1). At the active site SARS-CoV-2 Mp, rutin (BE = -9.098 kcal/mol), catechin (BE = -7.677 kcal/mol) and kaempferol (BE = -7.215 kcal/mol) have a better binding energy than the reference Remdesivir (BE = -7.194 kcal/mol) and Hydroxychloroquine (BE = -5.816 kcal/mol). As far as to the human furin protease target, five phenolic compounds (yellow in table 1) require less energy to bind than the two-drug references. Quercetin showed very promising anticovid effects *in vivo* tests with an IC_{50} of 73 µM against SARS-Cov 3CL(pro) (Nguyen et al. 2012) and 8.6 µM against SARS-Cov PL(pro) (Park et al. 2017). Also, several polyphenols compounds have been reported to show a good inhibition against SARS-Cov on 3CL protease targeted due to their hydrophobic aromatic rings and hydrophilic hydroxyl groups (Khaerunnisa et al. 2020; Jo et al. 2020). In this present study, we show that there are other interesting targets.

The 2-D visualization of the compounds for each target having a BE lower than at least one of two references, blue in table 1, is represented (Figure 2) and in 3D for those having a BE lower than the two references, yellow in table 1, (Figure 3). The docking analysis showed that **Quercetin** forms H-bonds with SARS-CoV-2 Mp amino acids Glu 166, Hie 164, Hie 163, Gln 189; with SARS-CoV-2 RBD amino acids Ile 358, Asn 388, and HF protease amino acids Glu 236, Leu 227, Ash 264, and Glh 257 (Figure 2A/B/C). **Catechin** forms H-bonds with SARS-CoV-2 Mp amino acids Glu 166, Hie 164; with SARS-CoV-2 RBD amino acids Ser 359, Asn 331, Cys 361, Ile 332, and HF protease amino acids Asp 306, Pro 256, and Asp 258 (Figure2A/B/C). **Rutin** forms H- bonds with SARS-CoV-2 Mp amino acids Glu 166, Leu

141, Thr 26; with SARS-CoV-2 RBD amino acids Asn 388, Asp 389, Ala 363, Cys 361, Ser 359, Ile 332, and Asn 331 and with HF protease amino acids Asp 153, Leu 227, Asn 295, Asp 258, and Gly 255 (Figure2A/B/C). **Kaempferol** forms H- bonds with SARS-CoV-2 Mp amino acids Glu 166, Gln 189, Hie 164; with SARS-CoV-2 RBD amino acids Ile 358, Asn 388, and HF protease amino acids Leu 227, Glh 257, Ash 264, and Glu 236 (Figure 2A/B/C). **Gallic acid** forms H-bonds with SARS-CoV-2 RBD amino acids Ser 359, Tyr 365, Leu 390, and HF protease amino acids Ser 253, Pro 256, and Asp 306 (Figure 2B/C). And finally **Piperitone** forms only unfavourable interaction with SARS-CoV-2 RBD amino acids Phe 392 (Figure 2B).

Rutin has the largest hydrogen bond with 15 H-bonds on all three targets followed by quercetin (10 H-bonds), catechin (9 H-bonds), kaempferol (9 H-bonds) and gallic acid (6 H-bonds). This high number of rutin binding is linked to its hydroxyl group richness (10 OH). Glycosylated phenolics have better docking than their corresponding aglucone (Sharma, Panigrahi, et Suresh 2014).

Furthermore, knowledge of the pharmacokinetic parameters and the degree of toxicity of the candidate compounds to become a drug is crucial. Computer simulation makes it possible to rule out molecules that would not respond to the above parameters at an early stage. First we used SwissADME to calculate ADME (absorption, distribution, metabolism, excoriation) according to Lipinski's and Veber's Rules. Only rutin and remdesivir have values beyond those defined by Lipinski's and Veber's Rules (Table 2). This is one of the reasons that remdesivir is not currently available for oral administration. Since the beginning of May 2020 the American administration has given its authorization for the use of this drug against covid 19. However its mode of intravenous administration does not facilitate rapid large-scale production and often requires hospitalization of the patient (US FDA 2020).

On the other hand, the admetSAR1 online server was used to determine toxicological properties. The studied compounds are non-carcinogenic (Table 3). In acute oral toxicity, β-Sitosterol is in category I (with LD50 ≤ 50mg/kg), quercetin and kaempferol in category II (50 mg/kg > LD50 < 500 mg/kg), Lupeol, rutin, gallic acid, piperitone and limonene in category III (500 mg/kg > LD50 < 5000 mg/kg) and finally catechine in category IV (LD50 values > 5000 mg/kg). Except β-sitosterol, none of the compounds displayed a risk of ames toxicity, carcinogenicity, acute oral toxicity, and rat acute toxicity (Table 3).

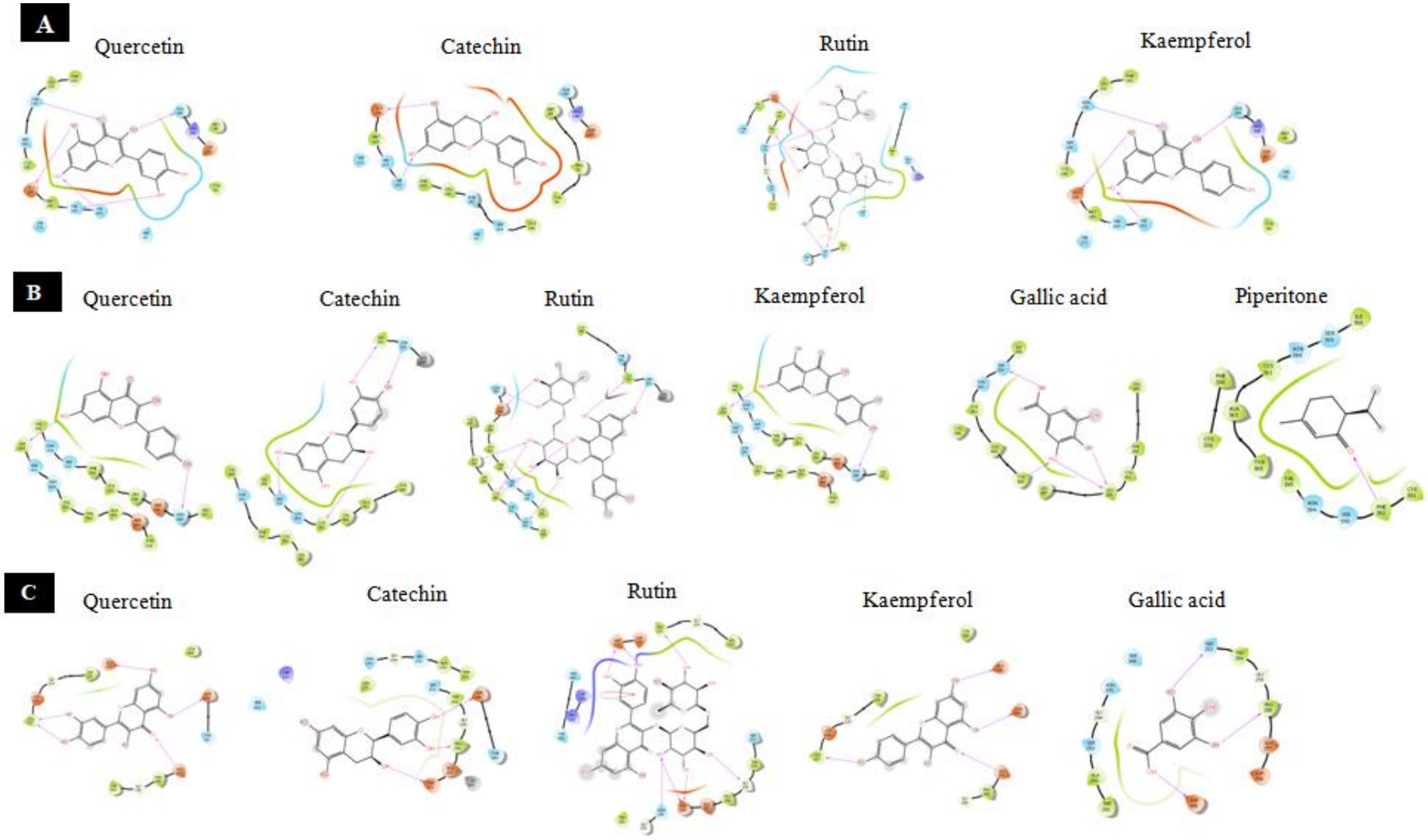


Figure 2 : 2D visualization of molecular interaction of SARS-CoV-2 main protease **(A)**, SARS-CoV-2 receptor binding domain **(B)** and human furin protease **(C)** with the biomolecules having at least better binding energy than one reference drug (hydroxychloroquine or/and Remdesivir).

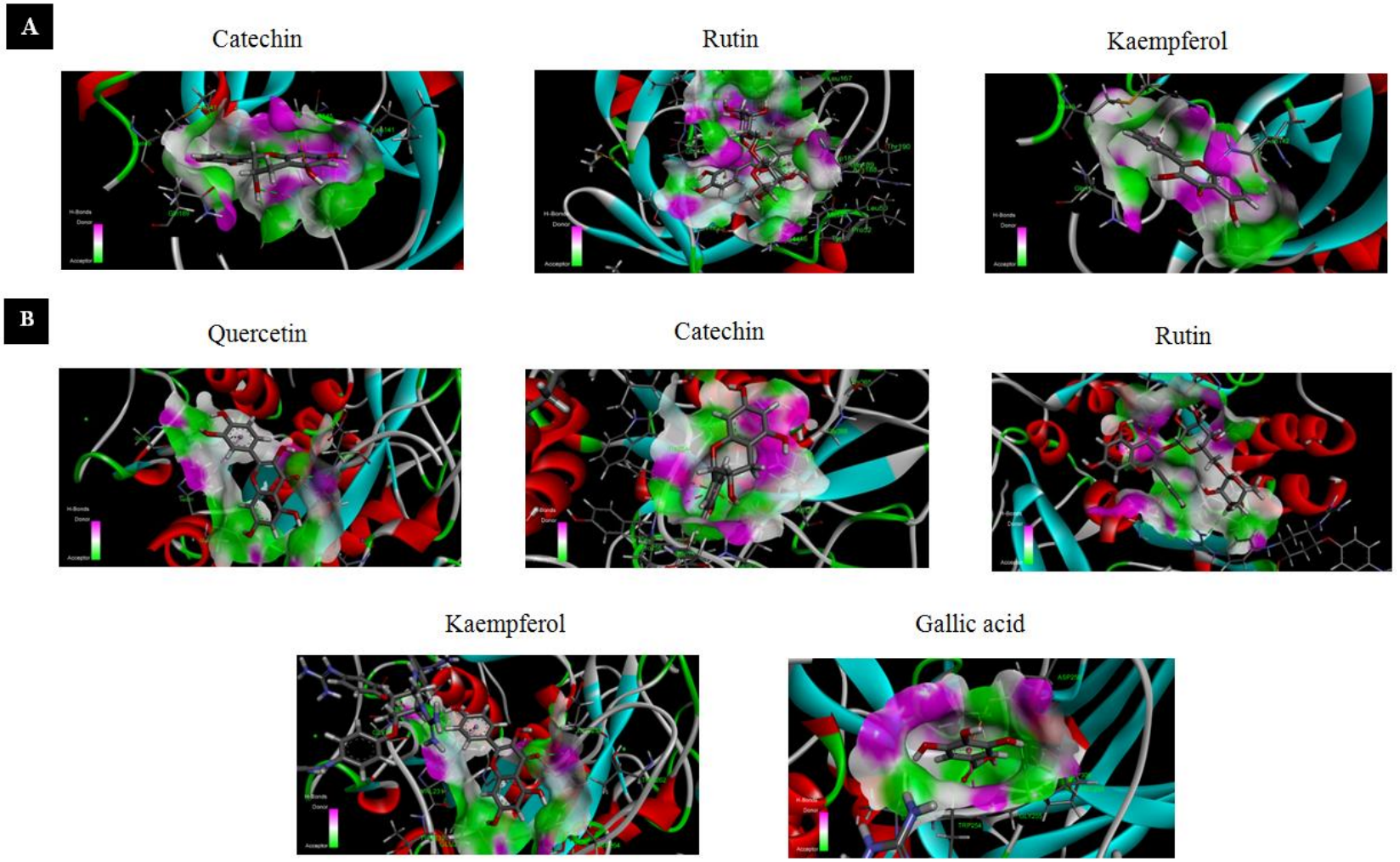


Figure 3: 3D visualization of docking analysis of SARS-CoV-2 main protease **(A)** and human furin protease **(B)** binding with the biomolecules having better binding energy than the two drug reference (hydroxychloroquine and Remdesivir)

Table 1: molecular docking of selected compound with target protein called SARS-CoV-2 main protease (Mp), SARS-CoV-2 receptor binding domain (RBD) and human furin protease.

Compound	SARS-CoV-2 Mp			SARS-CoV-2 RBD			human furin protease		
	BE (kcal/mol)	Glide Emodel	Glide Energy	BE (kcal/mol)	Glide Emodel	Glide Energy	BE (kcal/mol)	Glide Emodel	Glide Energy
β Sitosterol	**-3.646**	-35.362	-29.807	---	---	---	**-3.148**	-36.074	-30.661
Quercetin	**-7.169**	-63.742	-46.679	**-6.308**	-56.413	-41.346	**-5.988**	-49.649	-37.044
Catechin	**-7.677**	-69.744	-48.004	**-6.470**	-58.673	-43.239	**-5.856**	-56.369	-41.751
Lupeol	**-3.079**	-28.121	-24.988	**-2.952**	-30.678	-26.349	**-2.777**	-27.695	-23.697
Rutin	**-9.098**	-101.463	-71.94	**-7.601**	-88.545	-67.123	**-5.745**	-77.014	-57.839
Kaempferol	**-7.215**	-59.056	-42.910	**-6.743**	-56.693	-41.205	**-5.624**	-45.854	-33.642
Gallic Acid	**-5.441**	-43.604	-32.518	**-5.767**	-42.971	-32.428	**-5.732**	-45.735	-33.766
Piperitone	**-5.670**	-28.637	-21.622	**-5.937**	-30.566	-22.562	**-3.544**	-20.472	-16.342
Limonene	**-5.234**	-23.826	-18.247	**-4.218**	-20.981	-16.712	**-2.700**	-16.444	-14.181
Remdesivir *	**-7.194**	-7.713	-57.238	**-7.851**	-88.041	-65.536	**-5.544**	-68.253	-53.984
Hydroxychloroquine*	**-5.816**	-54.822	-42.432	**-4.828**	-44.138	-37.550	**-4.277**	-44.157	-37.096

*Remdesivir and Hydroxychloroquine used as references. *Blue:* Docking Score Is greater than Hydroxychloroquine; *Yellow:* Docking Score Is greater than Remdesivir and Hydroxychloroquine

Table 2: Physicochemical properties of the selected compounds for good oral bioavailability by **SwisADME.**

Compounds	**Lipinski Rules**				**Lipinski's Violations ≤1**	**Veber Rules**	
	MW (g/mol) <500	**HBA <10**	**HBD <5**	**Log P ≤5**		**nRB ≤10**	**TPSA ≤140**
Beta Sitosterol	414.71	1	1	9.34	1	6	20.23
Quercetin	302.24	7	1	1.54	0	1	131.36
Catechin	290.27	6	5	0.36	0	1	110.38
Lupeol	426.72	1	1	9.87	1	1	20.23
Rutin	610.52	16	10	-0.33	3	6	269.43
Kaempferol	286.24	6	4	1.90	0	1	111.13
Gallic Acid	170.12	5	4	0.70	0	1	97.99
Piperitone	152.23	1	0	2.85	0	1	17.07
Limonene	136.23	0	0	4.57	0	1	0.00
Remdesivir	**602.58**	**12**	**4**	**1.91**	**2**	**14**	**213.36**
Hydroxychloroquine	**335.87**	**3**	**2**	**3.58**	**0**	**9**	**48.39**

MW: molecular weight, *HBA:* hydrogen bond acceptor, *HBD:* hydrogen bond donor, *Log P:* lipophilicity, *AMR:* molar refractivity; Ro5V- Rule of five violation.

Table 3: Toxicological properties of the selected compounds BY **admetSAR**.

Compound	**Parameters**			
	Ames Toxicity	**Carcinogens**	**Acute Oral Toxicity**	**Rat Acute Toxicity**
Beta Sitosterol	NAT	NC	I	2.6561
Quercetin	NAT	NC	II	3.0200
Catechin	NAT	NC	IV	1.8700
Lupeol	NAT	NC	III	3.3838
Rutin	NAT	NC	III	2.4984
Kaempferol	NAT	NC	II	3.0825
Gallic Acid	NAT	NC	III	1.8670
Piperitone	NAT	NC	III	1.8246
Limonene	NAT	NC	III	1.4819
Remdesivir	**NAT**	**NC**	**III**	**2.7169**
Hydroxychloroquine	**AT**	**NC**	**III**	**2.6348**

NAT: Non Ames toxic; **NC:** Non-carcinogenic; (Category-I compound with LD50 ≤ 50mg/kg. Category **II** compounds with LD50 values > 50mg/kg and < 500 mg/kg. Category **III** compounds with LD50 values >500mg/kg and < 5000 mg/kg. Category **IV** compounds with LD50 values > 5000 mg/kg).

Conclusion

The Covid 19 currently presents a major challenge in human health. To treat this viral infection different treatments are being tested without getting the real cure so far.

In this present study, we evaluated by *In silico* test (pathogen-therapeutic molecule target modeling) the therapeutic potential of the biomolecules isolated from three Djiboutian medicinal plants, namely *Acacia seyal, Cymbopogon commutatus* and *Indigofera caerulea.*

Phenolic compounds give the best preliminary results with minimized docking scores. On the three targeting sites, rutin has better binding energy than the two drug references Hydroxychloroquine and Remdesivir.

This encouraging result must be confronted with *in vitro* and *in vivo* tests to determine the real performance of these biomolecules in the fight against the coronavirus and before clinical trials in humans can be performed.

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