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Research Article

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In Silico Study of the Potential Inhibitory Molecules Isolated from SCOPARI a Dulcis L. (Scrophulariaceae) on the MPro Protease of the COVID-19 SARSCoV-2 Virus

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ABSTRACT

COVID-19 has posed a global threat, causing enormous economic, political and social consequences. Although vaccines are in full use around the world, the search for drugs against COVID-19 continues. Molecular docking is an in-silico method offering an alternative to research and new drug discovery and helps to reduce the time and cost of research. The objective of our study is to research by molecular docking the neutralizing potentials of the Mpro protease of SARSCoV-2 by phyto-molecules isolated from Scoparia dulcis.

Our analysis focused on 35 biomolecules of which we deepened their affinity, visualize the types of interactions with the amino acid residues of the protease, as well as their bioavailability. This study shows that 20 biomolecules have an interaction affinity on the protease better than remdesivir and nelfinavir (reference molecules whose effectiveness on COVID-19 disease has been approved). They consist of 9 flavonoids ((lutéoline, cynaroside, gossypine, scutellaréine, hydroxytetramethoxyflavon, vitexine, scutellarin, hispiduline-7-glucuronide, cirsimarine,); 7 diterpenes (scoparic acid A, B, C, scopadulciol, scopaduline, scopadulcic acid A and B); and 2 triterpenes (friedelline and glutinol). These molecules are likely to interact more easily with the protease than remdesevir and nelfinavir. Among the latter, those which present a significant interaction consist mainly of 7 flavonoids (cirsimarin, hispidulin-7-glucuronide, vitexin, hydroxytetramethoxyflavone, gossypotin, cynaroside) and 1 diterpene (glutinol). Their inhibitory capacity is justified by the fact that they interact with methionine 6 and tyrosine 126 of the main protease of SARSCoV-2. These two amino acids participate in the vital interactions of protease dimerization, which makes these molecules dimerization neutralizers.

In view of our analysis results, we accept the hypothesis that the molecules virtually presenting an inhibitory activity of dimerization, with a better affinity on the protease than remdesevir and nelfinavir are potential drugs against COVID-19

Keywords: COVID-19, Molecular Docking, Main Protease, Phyto- Molecules, Affinity, Dimerization

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. It is a new virus that emerged in China in December 2019 and rapidly spread around the world, causing a pandemic that has severely strained healthcare capacity. The pandemic has caused enormous political, economic, and social consequences, with more than 537.5 million cases and 6.31 million deaths recorded worldwide as of June 2022 [1].

SARS-CoV-2 has been identified as an enveloped, positive-stranded RNA zoonotic virus possessing glycoproteins and belonging to the Coronaviridae family. It is similar to severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus. Among all known RNA viruses, coronaviruses have the largest genomes ranging from 26 to 32 kb in length [2].

The SARS-CoV-2 genome encodes two polyproteins, pp1a and pp1ab, and four structural proteins (3-4). The polyproteins are cleaved by the critical SARS-CoV-2 main protease (Mpro or Mpro SARS-CoV-2, also known as 3CL protease) at 11 different

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sites to produce shorter non-structural proteins vital for viral replication [5-6].

The main protease of SARS-CoV-2 is a widely exploited target protein for inhibitor research. It consists of three domains, a chymotrypsin-like domain I, a picornavirus 3C protease-like domain II, and a domain III, consisting of 5 antiparallel α-helices that regulates dimerization. Dimerization is essential for the enzymatic function of MPro. The binding pocket of Mpro is located between domains I and II, with a catalytic Cys-His dyad functioning as the active site. Mpro targets a Leu- Gln ↓ (Ser, Ala, Gly) recognition sequence (with ↓ designating the cleavage site). No known human protease has the same cleavage specificity as Mpro and is an ideal target for therapeutic development [7-8].

When an inhibitor binds to an active site, it prevents substrate binding, completely inhibiting the action of the protease. Inhibition of protease activity is possible by targeting either the active site of the catalytic dyad or the active site of dimerization [9].

The lack of treatment during the pandemic has led to the repositioning of some antivirals. Ensitrelvir, Simnotrelvir and Nirmatrelvir are drugs targeting Mpro and approved for administration in some countries [10-12]. Other drugs such as remdesivir, hydroxychloroquine, ivermectin have also been used during the pandemic against SARS-CoV-2 [13].

In silico methods offer an alternative for research and development, and their use has become essential throughout the process of developing a new drug. With the advent of Covid-19, these methods have been in high demand by the scientific world in research as well as in the repositioning of drugs that can limit the spread of the disease [14].

Also called Structure-Activity-Relationship (SAR), these are study or testing methods that use computer tools, hence their name " in silico." It represents the relationship between the structure of a compound or a group of compounds and a biological effect. In silico methods are interesting in the medical field because they allow the evaluation of physicochemical properties, intermolecular binding capacity as well as the reactivity of molecules [15]. Its first uses in the pharmaceutical field date back to the second part of the 20th century where the relationship between the chemical structure and the pharmacodynamic and pharmacokinetic properties of compounds within biological systems were studied via computer tools [16]. In silico methods have led to enormous progress in many fields such as structural biology (X-ray crystallography, magnetic resonance), molecular biology and bioinformatics. Due to the rise of computer tools, the use of in silico tests in the medical world and especially in the pharmaceutical field has grown. There are several in silico methods classified into two categories: ligand-based methods (QSAR Quantitative-Structure-Activity-Relationship methods, pharmacophore) and receptor-based methods (molecular docking and molecular modeling) [17]. Their role is to virtually determine the biological effect of a molecule by relating the three-dimensional structures of a ligand and a receptor or by studying the structural similarity of molecules. Knowledge and quality of the structure of proteins and ligands are essential. The structure of proteins is mostly resolved by X-ray crystallography or Nuclear Magnetic Resonance (NMR) and stored in the large protein database (Protein Data Bank). In the absence of resolution, the structure of proteins can be obtained by sequence homologies [18-19]. There are several small molecule (ligand) libraries , the best known of which is Pubchem , managed by the National Center for Biotechnology Information (NCBI), which is a branch of the United States National Library of Medicine under the authority of the National Institutes of Health (NCI) [20]. It provides relevant information on the structures, physicochemical, pharmacological and toxicological properties of ligands. Ligands can also be drawn and saved in different formats (pdb, mol, mol2, sdf, etc.) by drawing inspiration from the structure of other ligands available in the literature using construction software such as ChemDraw, Arguslab, Titan or Sybyl [21].

Various categories of drugs from the group of antibiotics (norfloxacin, isoniazid and dorzolamide), antiretrovirals against HIV (ritonavir, saquinavir, amprenavir, indinavir), and some drugs like captopril, Furbiprofen were developed using in silico research techniques [22]. Molecular docking is the most widely used testing method in drug research and development. It is fast, inexpensive, and easy to implement [23]. Docking testing software Molecular are numerous and contain various search algorithms and scoring functions (Autodock, dock, Flex, Fred, Glide, Gold, Surflex -dock, Pro Leads) [24]. Autodock and Gold are the best software with the most efficient analysis algorithms. Autodock has been used in a relevant way in the preclinical development of the molecule raltegravir (HIV integrase inhibitor) whose distribution on the American market was authorized in 2007 [25].

For our research we used the molecular docking assay technique. It consists of determining the relative position of a ligand on a receptor or biological target. Each possible position is associated with an energy also called a score. The most likely complex formed is the one that minimizes this energy [26]. The principle of docking is based on two complementary steps: first, the search for conformations of the ligand that can establish an ideal interaction with the biological target; then, the sorting of these poses using a score function that associates them with an estimated interaction energy. There are three categories of docking, classified according to the flexibility of the molecules: flexible docking, semi-flexible docking and rigid docking. Molecular docking is most often associated with Lipinski 's rule to predict the bioavailability of a drug when taken orally. It was described by Lipinski et al and allows rapid identification on a large scale of molecules with a Drug- like character more likely to present the bioavailability characteristics necessary for the development of a drug candidate. Lipinski 's rule provides threshold values for molecular weight (≤ 500), number of hydrogen bond donors (≤ 5) and acceptors (≤ 10), and water/ octanol partition coefficient (≤ 5). Although Lipinski 's rule is the best known, the Veber and Ghose-Viswanadhan-Wendoloski rules are also used to identify the drug- like character of a molecule [27-29].

The study ligands represent the natural molecules of the Scoparia dulcis L. This choice is justified by the fact that Scoparia dulcis L is widespread in tropical and subtropical areas and is one of the plants used to treat the most well-known disorders of Covid-19

such as fever, cough, and fatigue [30]. A number of different principles such as scoparic acid A, scoparic acid B, scopadulcic acid A and B, scopadulciol and scopadulin have been shown to contribute to the observed medical effect of the plant. These molecules have been shown to possess interesting antiviral, antitumor, and antimicrobial activities [31].

Our work is to research the biomolecules of Scoparia dulcis L may be potential inhibitors of the main protease of SARS-CoV-2 by the molecular docking assay technique. To do this, we will explore and then compare the modes of interaction of biomolecules with the Mpro protease. This research will provide a rapid discovery of potential inhibitors of SARS-CoV-2 Mpro.

Materials and Methods

Selection of Ligands

Scoparia biomolecules dulcis L. were selected through a literature search of articles published in PubMed, Sciences Direct, and Google schoolar and describing the extraction and identification processes. The compounds separated from the polar extracts (water, alcohol) were chosen for our studies. This choice is linked to the way the plant is used (decoction) to treat the most well-known symptoms of covid 19 (cough; fever; fatigue) (30). The three-dimensional structures of the selected biomolecules were collected from the Pubchem repository (https://pubchem.ncbi. nlm.nih.gov/) in SDF (Structure Data File) format.

Preparation of Ligands

Autodock Tools was used to optimize the selected ligands. Since SDF structures are not supported by Autodock Tools, Open Babel (algorithm contained in pyrx) was used to convert SDF structures to PDB format. Ligand preparation consisted of adding partial gastainer charges; adding polar hydrogens and adjusting the number of rotatable bonds. The prepared ligands were registered in our chemical library in 3D PDBQT format.

Preparation of Protease

The main protease of SARS-CoV-2 in its mature form (ID 7kph) was used as a receptor target for Scoparia biomolecules dulcis L. It was solved by X-ray diffraction with a resolution of 1.46 A. The crystal structure of the protease was obtained from the large protein database (http://www.rcsb.org) in pdb format.

Protein preparation involves removing water molecules, adding Kolman charges and polar hydrogens using Autodock Tools.

Molecular Docking

Autodock vina was used in all molecule docking experiments. Computational docking is performed to generate a population of promising ligand orientations and conformations within the binding site. Since the target protein is not coupled to an inhibitor, we performed a semi-flexible blind docking in which the flexible ligand traverses the conformational space of the target protein, considered rigid. The center of the fixed grid X=14.24 Y=2.14 Z=3.49 is large enough to encompass all possible ligand-protein complexes. The compounds were evaluated individually during docking and before their first interaction, the classical MM2 force field was applied to optimize the structures of these small molecules, thus ensuring the rigidity of their active sites. Finally, the studies of the ligand-protein complexes interactions were carried out using the Biovia program discovery studio 4.5. This analysis produces a result describing the different bonds (hydrophobic, hydrogen, van der Walls) and the bond length of each pose.

Medicinal properties of Ligands

The probability that a molecule is orally medicated is indicated by Lipinski 's rule of five parameters. The druggability of ligands ensures adequate plasma concentration and the desired level at the site of action. The concept of Druggability or Drugglikness was developed by Christophe LIPINSKI who established an empirical rule based on the physicochemical properties of drugs taken orally. This rule, called Lipinski's rule of five, is a standardized parameter for detecting oral drugs and estimating the potential for drug design from biomolecules. The rule of five is based on four physicochemical parameters for the molecule to have adequate pharmacokinetic properties:

- Molecular weight (<500g/mol)
- octanol partition coefficient Log P (Log P<5)
- The number of hydrogen bond donors (<5),
- The number of hydrogen bond acceptors (<10).

The pharmacokinetic parameters of the selected biomolecules were studied with the SWISSADME server (www.swissadme.ch/index.phpm). The structures of the molecules are transmitted to the online server for launching the calculations after having carried out the conversion into SMILES format (simplified Molecules that meet at least three of the parameters are likely to have good bioavailability.

Results

Ligand

We obtained 35 isolated biomolecules from polar extract of Scoparia parts dulcis L. These molecules consist of 19 flavonoids, 7 diterpenes, 4 triterpenes, 2 glycosides, and 3 other molecules (an alkaloid, a steroid, and a vitamin). The study ligands and their structures have been represented in the tables below.

Table 1: 2D structure of reference molecules

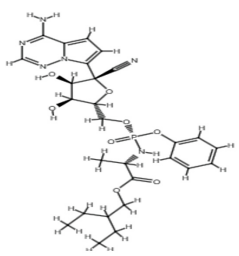
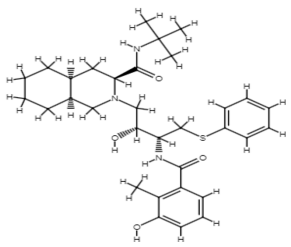
Remdesivir 	Nelfinavir 

Table 2: Structure 2D des Flavonoïdes

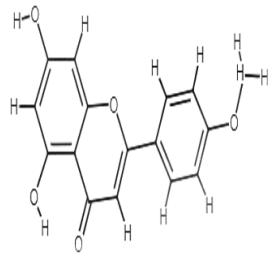
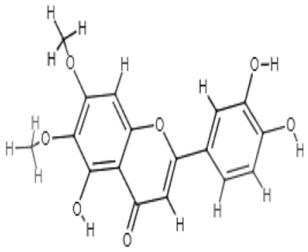
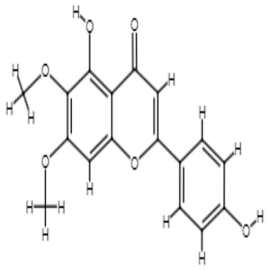
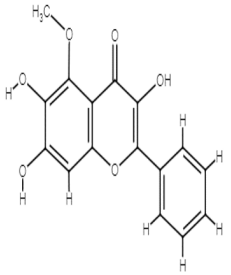
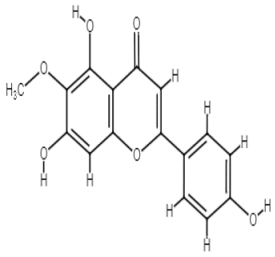
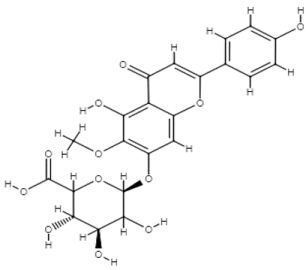
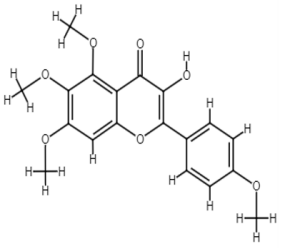
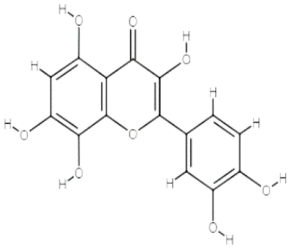
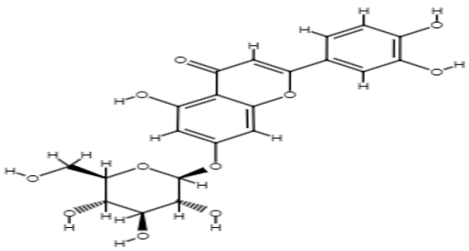
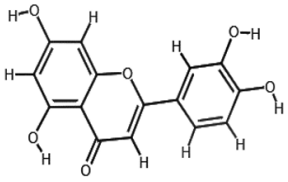
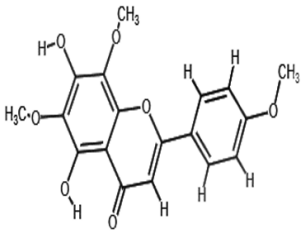
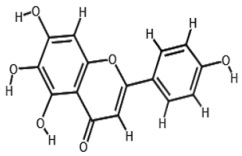
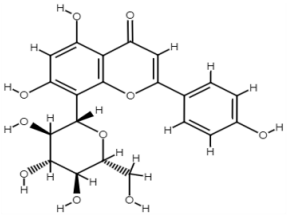
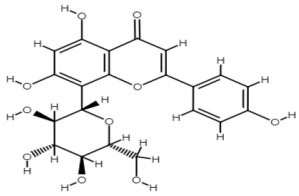
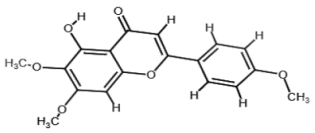
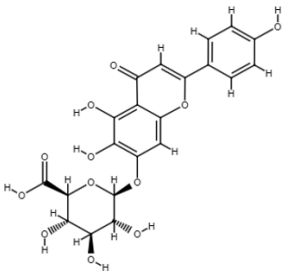
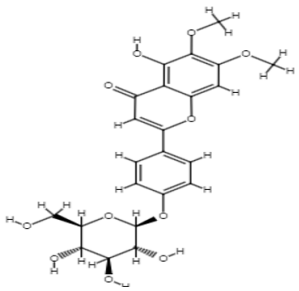
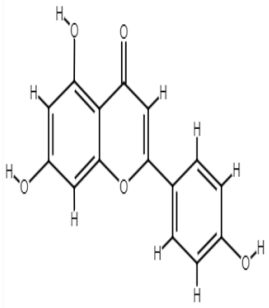
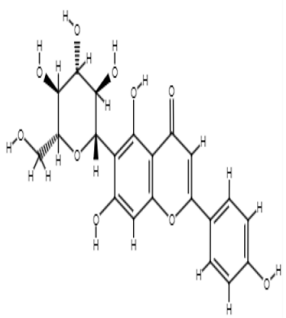
 Acacetin	 Cirsiliol	 Cirsimaritine	 Dihydroxy-dimethoxyflavone
 Hispiduline	 Hispiduline 7-glucuronide	 Hydroxytetramethoxyflavone	 Gossypetine
 Cynaroside		 Luteoline	 Nevadensine
 Scutellarein	 Vicenine 2	 Vitexine	 Salvigenin
 Scutellarin	 Cirsimarine	 Apigenine	 Isovitexine

Table 3: Structure 2D des diterpènes

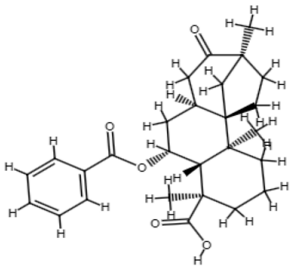
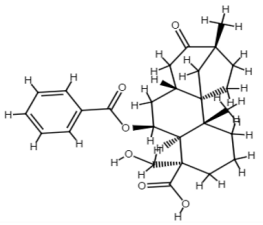
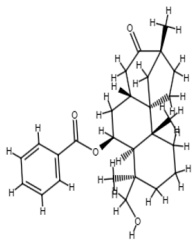
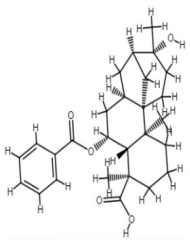
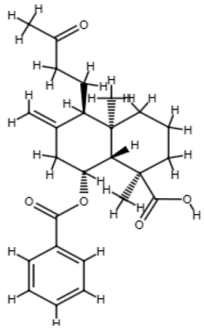
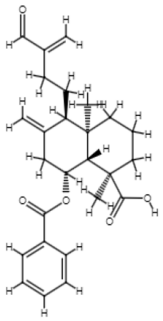
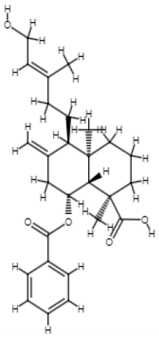
			
Acide Scopadulcique B	Acide Scopadulcique A	Scopadulciol	Scopaduline
			
Scoparic Acid B	Scoparic Acid C	Scoparic Acid A	

Table 4: 2D structure of triterpenes

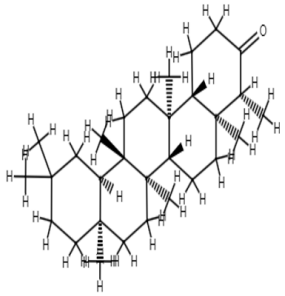
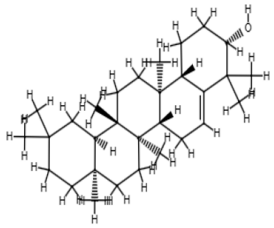
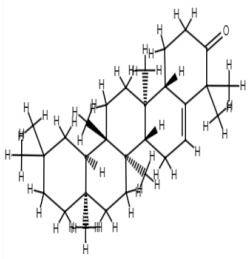
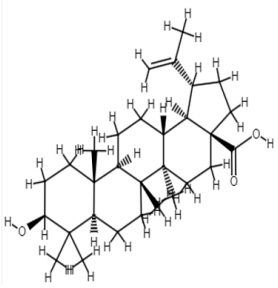
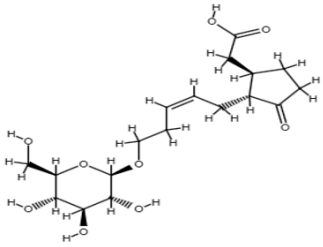
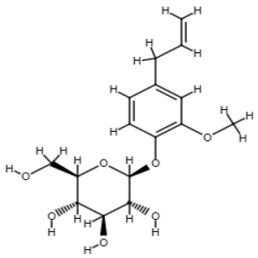
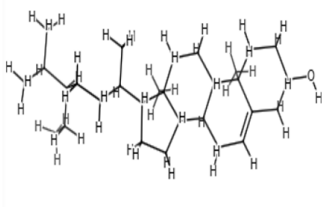
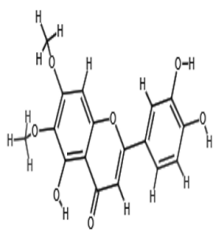
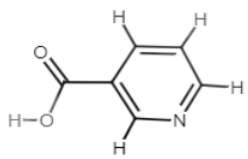
			
Friedeline	Glutinol	Glutinone	Betulic acid

Table 5: 2D structure of glycosides

		
Acid glucoside tuberonic	Eugenyl glucopyranoside	
Steroid	Alkaloid	Vitamin
		
sitosterol	Coixol	Nicotinic acid

Molecular Docking

I-Bond energy

The binding energies obtained during molecular docking tests of phytomolecules with the Mpro protease present energetic values between -5.7 and -8.8 Kal /mol. Scopadulcic acid B presented the lowest interaction energy (-8.8 Kcal/mol) among the biomolecules studied. For the reference molecules, the study Binding energies presented respectively -7.5 and -6.8 kcal for remdesivir and nelfinavir. A comparative analysis of the energetic values of the study molecules shows that among the 35 phytomolecules studied, 21 phytomolecules had lower interaction energies with the main protease than the two reference molecules. All biomolecules are classified in order of growth in the table below according to their binding energy (Table VI).

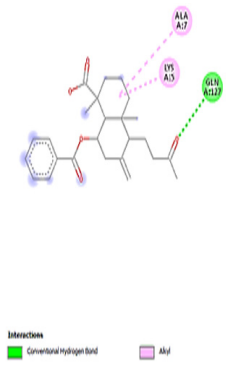
Table 6: Results of the binding energies

Molecules	Affinity (Kcal/Mol)
Nicotinic acid	-5.7
Isovitexin	-6.1
Dihydroxy-dimethoxyflavone	-6.1
Coixol	-6.2
Nelfinavir	-6.8
Salvigenin	-6.8
β -Sitosterol- β -D-glucoside	-7
Cirsiliol	-7.1
Cirsimaritine	-7.1
Hispidulin	-7.1
Nevadensin	-7.1
Tubercular acid glucoside	-7.2
Glutinin	-7.3
Apigenins	7.4
Vicenine 2	7.4
Remdesivir	-7 ;5
Acacetine	7.5
Acid scoparique B	7.6
Fucking Acid A	-7.6
Cirsimarine	-7.7
Hispiduline 7 glucuronide	-7.8
Betulic acid	-7.8
Acid scoparique C	7.9
Scopaduline	-7.9
Scutellarin	-7,9
Vitexine	-8
Hydroxytetramethoxyflavone	-8
Scopadulciol	-8
Eugenyl-pyranoside	-8
Scutellarein	-8
Gossypetin	-8
Cynaroside	-8,1
Acide scopadulcique A	-8,2
Luteoline	-8,4
Friedelline	-8,5
Glutinol	-8,7
Acide scopadulcique B	-8,8

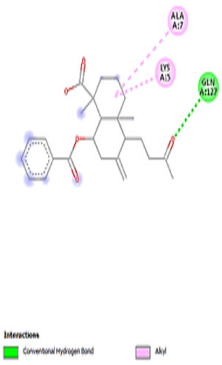
Visualisation des interactions

Visualization of ligand-receptor complex interactions shows the types of interactions formed as well as the amino acids engaged with the phytomolecules. In our study, all phytomolecules had a measurable interaction with the active residues of the protease. The amino acid residues of the protease engaged in interactions with the ligands are: Ser 113, Gln 127, Tyr 126, Phe 112, Lys 5, Cys 128, Met 6, Ala 7, Val 125, Thr 111, Val 114, Tyr 128, Phe 291, Phe 112. Table II shows the result of the ligand-receptor complexes formed.

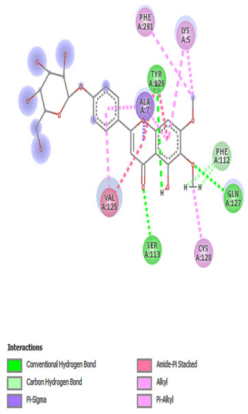
Table 7: Results of ligand-receptor interactions



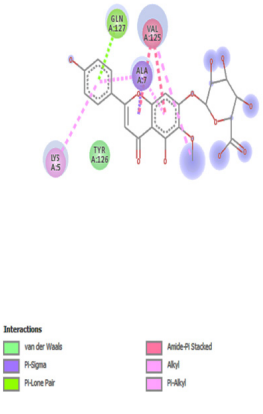
Scoparic acid B



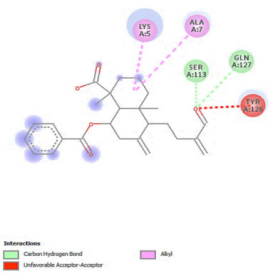
Acice scoparic A



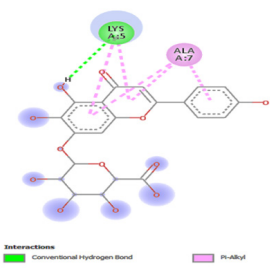
Cirsimarine



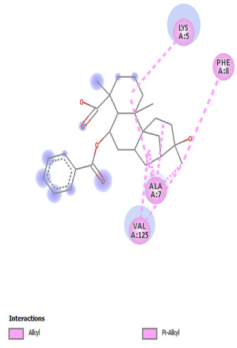
Hispidulin 7-glucoside

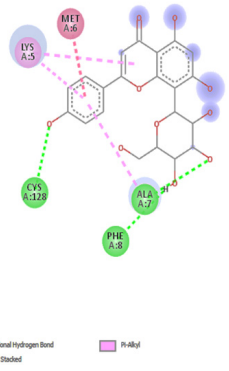


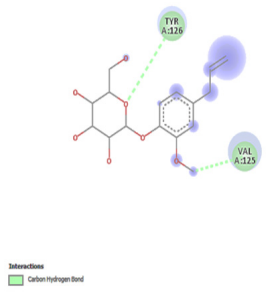
Scoparic acid C

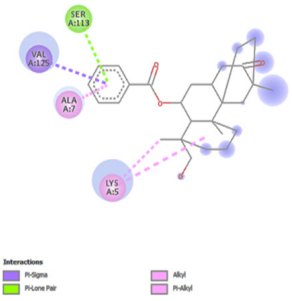


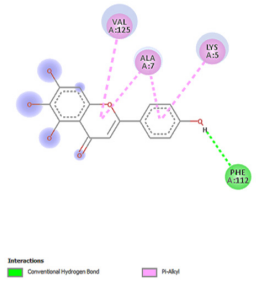
Scutellarin

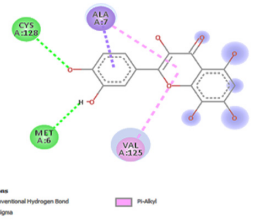

Scopadulin

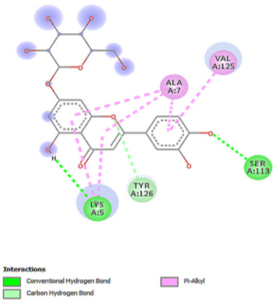

Hydroxytetramethoxyflavone

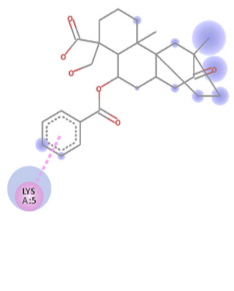

Eugenyl-pyranoside

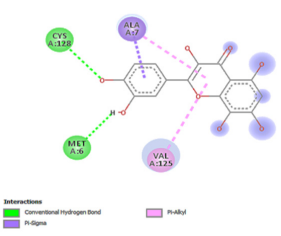

Scopadulciol

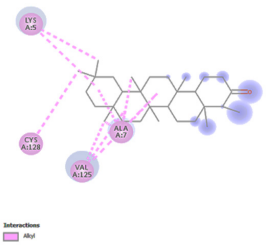

Scullarein

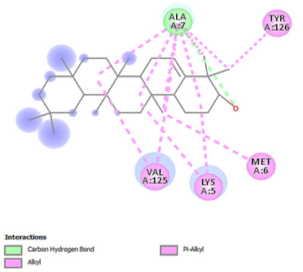

Gossypotin

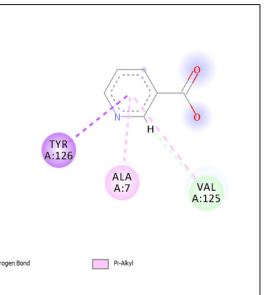

Cynaroside

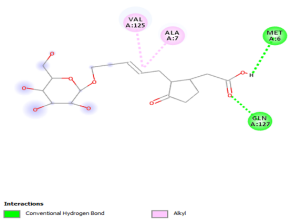

Scopadulcic acid A

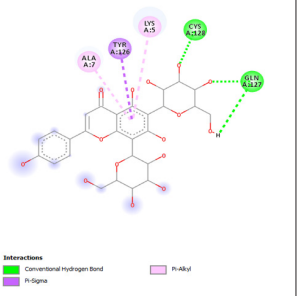

Luteolin

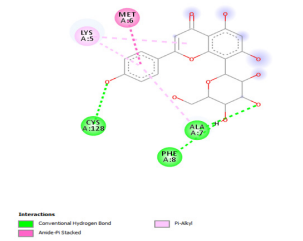

Friedeline

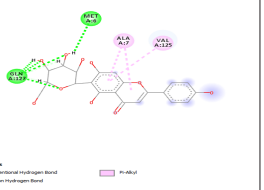

Glutinol

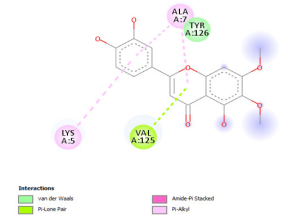

Nicotinic acid

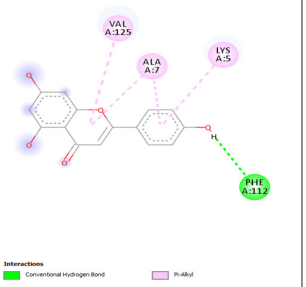

Tuberonic acid glucoside


Vicenine 2

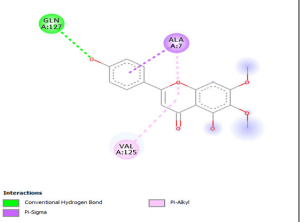

Vitexin

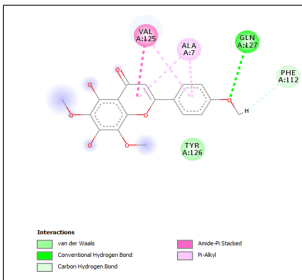

Isovitexin

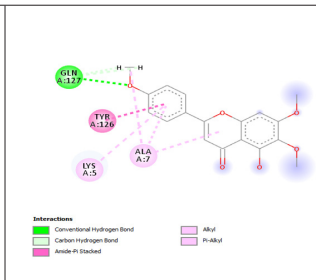

Cirsiliol

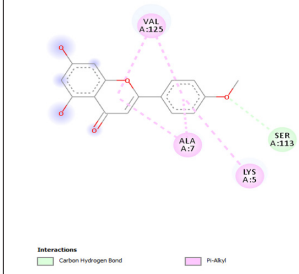

Apigenin

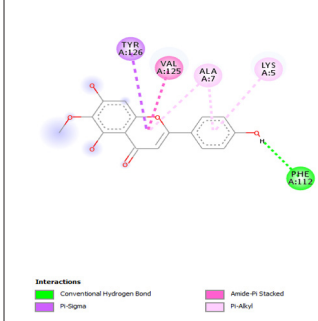

Dihydroxy - dimethoxyflavone

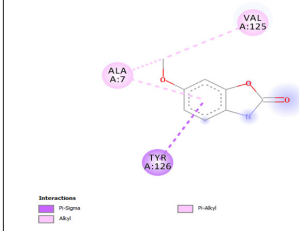

Cirsimaritine

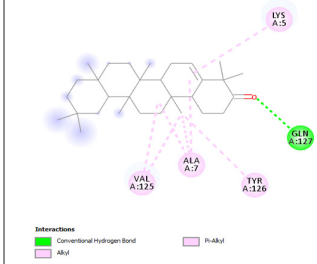

Nevadensin

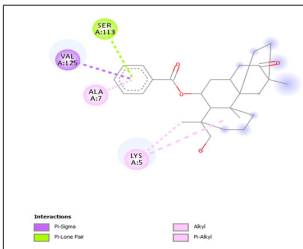

Salvigenin

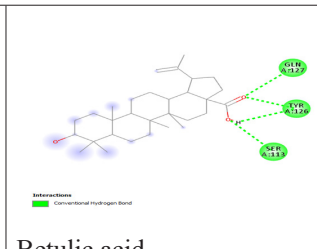

Acacetin

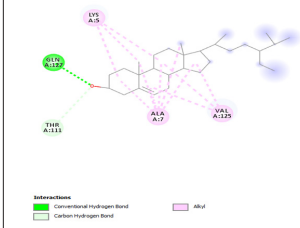

Hispidulin


coixol


glutinone


Scopadulciol


Betulic acid


Sitosterol

Like Property or Character

The study of the druglike character by Lipinski ‘s rule shows us that among the ligands studied, 4 biomolecules do not satisfy Lipinski ‘s rule (vicenin 2, hispidulin 7 glucoside, scutellarin). These biomolecules only respect one or two physicochemical criteria (table 3).

Table 8: Physicochemical criteria

Molecules	Molecular weight (<500 g/mol)	Hydrogen bond donors (<5)	Hydrogen bond acceptors N (<10)	Coefficients From Log P sharing (<5)	Number of offense	Meet the criteria
Nicotinic acid	123.11	1	3	0.4	0	Yes
Acid glucoside Tuberonic	388.4	5	9	1.2	0	Yes
Vicenin 2	594.5	11	15	2.3	3	No
Vitexin	432.4	7	10	0,2	1	Oui
Isovitexin	432,4	7	10	0 ,2	1	Oui
Hispiduline 7-Glucoside	476,4	6	12	1,1	2	non
Cirsimarin	476,4	5	11	1 ,2	1	Oui
Luteoline	286,24	4	6	1,4	0	Oui
Cirsiliol	330,29	3	7	2,6	0	Oui
Apigenine	270,24	3	5	1,7	0	Oui
Dihydroxy-dimethoxyflavone	304,14	2	5	1,3	0	Oui
Circimartine	314,14	2	6	2	0	Oui
Nevadensin	344,3	2	7	2,9		Oui
Salvigenin	328,3	1	6	2,4	0	Oui
Hydroxytetra-methoxyflavone	356,3	1	7	2,9	0	Oui
Acacetin	284,26	2	5	2,1	0	Oui

Glutinol	426,7	1	1	9,2	1	Oui
Scopaduline	440 ,6	2	5	5.2	0	Yes
Scopaduciol	426.6	2	4	5.7	0	Yes
Fucking Acid A	440.6	2	5	5.7	0	Yes
Acid scoparique B	412.5	1	5	4.4	0	Yes
Acid scoparique C	424.5	1	5	5.3	0	Oui
Acide scopadulcique A	454 ,6	2	6	4	0	Oui
Acide scopadulcique B	438,6	1	5	5,2	0	Oui
Coixol	165,15	1	3	1,1	0	Oui
Friedelin	426,7	0	1	9,8	1	Oui
Glutinone	424.7	0	1	8.9	1	Oui
Acide betulique	456,7	2	3	8,2	1	Oui
Eugenyl-glucoside	326,34	4	7	0	0	Oui
Beta-sitosterol	414,7	1	1	9,3	1	Oui
Hispiduline	300,26	3	6	1,7	0	Oui
Scutellarein	286,24	3	6	1,7	0	Oui
Acide betulique	456.7	2	3	8,2	0	Oui
Scutellarin	462,4	7	12	0,8	2	non
Gossypetin	318,23	6	8	1,8	1	Oui

Discussion

Bioinformatics is widely used to improve drug design and predict drug interaction with macromolecules. The docking method consists of searching for interaction sites across the entire macromolecular surface. Therefore, the main protease of SARS-CoV-2 in its mature form uncoupled with a specific inhibitor ID 7kph was used for blind analysis of selected bioactive substances of the plant.

in silico assays, any molecule is likely to be a good inhibitor if it has the lowest binding energy (good affinity) and considerable interaction with the engaged amino acid residues of the biological target. In other words, although affinity is the ease with which a drug binds to its receptor, it does not alone define the potency of a drug. Indeed, the latter is also a function of its ability to produce a biological response [32].

Two molecules were used as references in the exploitation of our molecular docking results (remdesivir and nelfinavir). Previous studies show that these two molecules were active in silico and in clinical trials on the SARSCoV-2 virus. Remdesivir was the first antiviral approved by the FDA in the United States and was used for the management of hospitalized patients aged over 12 years (33). Hirofuni Ohashi et all 2021 demonstrated the in vitro efficacy of nelfinavir in decreasing the viral load of SARS-CoV-2 (34). The study of the energies of biomolecules of Scoparia dulcis L. with 7kph reveals to us 20 biomolecules (Acid, scopadulcic B, glutinol , friedellin , luteolin , scopadulcic acid A, cynaroside , gossypotin , scutellarein, eugenylpyranoside, scopaduliol, hydroxytetramethoxyflavone, vitexin, scutellarin, scopaduline, Acid scoparic C, betulic acid , hispidulin-7-glucuronide, cirsimarin, acid scoparic acid B, scoparic acid A,) (Table II) which has a good affinity than remdesivir and nelfinavir . These biomolecules are potential inhibitors of SARS-CoV-2 if they present a significant interaction.

The design of an anti-SARSCoV-2 drug is essentially based on the inhibition of the entry of the virus into the host cell (targeting ACE-2 receptors) and also the inhibition of the catalytic activity of the main protease (targeting the dyad catalytic or sub-S1-S5). Numerous reports on the design of inhibitor against SARSCoV-2 Mpro are based primarily on targeting the substrate binding pocket (blocking catalytic activity). However, there are allosteric sites that can be exploited for the development of anti-SARSCOV-2 inhibitors. The allosteric inhibition mechanism of Mpro occurred at the distal site or at the dimerization sites [35,36].

The distal site is located away from the catalytic site, in the interface region between domain I and II. It consists of five Arg contacts 131 - Thr 199, Arg 131 - Asp 289, Pro 132 - Thr 196, Asp 197 and Thr 198 - Asn 238, Tyr 239 -Leu 287 important in protease activity [37].

dimerization site consists of a number of key residues important in the dimerization mechanism: Arg4, Ser10, Gly11, Glu14, Asn28, Ser139, Phe140, Ser147, Glu290 and Arg298. These residues function cooperatively to control dimerization and maintain the integrity of the dimer interface [38,32].

Also, the N terminus of the protease (residues 1-7) plays an important role in dimerization [39]. The most important residues in this chain are Arg 4 and Met 6; they ensure the stability of dimerization (40,41) (13,14). Daniel W. Knelle et all 2020 reveals by crystallography that residues Gly 2, Tyr 126; Arg 4, Lys 13 7 and Leu 286 are involved in vital interactions for dimerization [42].

All of these allosteric sites of Mpro SARSCOV-2 constitute an alternative for the development of an inhibitor that is more resistant to the mutation phenomenon than the active site [43].

Visualization of the interaction types and the involved amino acid residues of the Mpro protease reveals that the biomolecules belong to domains I (8-101) and II (102-185). These residues play an important role in the formation of the active site and provide binding sites for inhibitors.

The results of intermolecular interactions of biomolecules with Mpro 7Kph show no interaction with the catalytic dyad (Cys 145 and His 41) nor with the active subunits of the S1-S5 protease. Thus, the biomolecules under study are not inhibitors of the catalytic activity of the Mpro protease. However, they presented significant interactions with Tyr 126 and Met 6 (key residues of dimerization).

In our study, the phytomolecules that inhibit dimerization by interfering with tyrosine 126 are: cirsimarin, cynaroside, eugenyl -pyranoside and hispidulin -7-glucoside. Also with methionine 6, gossypotin, luteolin and vitexin showed a measurable interaction.

The docked molecules were subjected to ADME analysis by Lipinski ‘s rule. We identified four molecules scutellarin, linarin, vicenin, hispidulin 7 glucoside which have low bioavailability.

Based on our analytical results, we assume that cirsimarin, cynaroside, eugeny -pyranoside, hispidulin -7-glucoside, gossypotin, luteolin and vitexin are potential inhibitors of the SARSCoV-2 virus by inhibiting the dimerization activity of the main protease Mpro. Thus, a polar or hydroalcoholic solution could be used to treat covid-19. This requires further investigations to confirm our results.

Furthermore, our research is in agreement with certain studies which approve the inhibitory potential of Mpo SARSCOV-2 of certain molecules studied. These include vitexin in a virtual screening test carried out by Shiv Rakesh and All (2021) (44). Also according to Anna Gaelle et all (2020) gossypetin is a potential inhibitor of SARS-CoV-2 in a computational study carried out (45). The inhibitory potential of luteolin has been approved by an in silico study (46) . Also luteolin is one of the main active ingredients continues in artemisia annua used for the treatment of Covid 19 (47).

Conclusion

In order to contribute to the search for a drug against covid-19, especially based on medicinal plants, we carried out a molecular docking test of biomolecules isolated from Scoparia dulcis L. on the main protease of SARS-CoV-2. The 7kph protease was used as an effective key target to inhibit the novel coronavirus. Among the studied biomolecules, 21 had a high affinity on 7kph Mpro than the reference molecules. The study of the bioavailability of the biomolecules shows that 4 biomolecules from the plant have a low bioavailability. Based on the intermolecular interactions and binding affinities with 7kph Mpro , the selected potential inhibitors are allosteric inhibitors of the protease activity. These results provide a direction for drug research against covid 19, which requires further investigations for drug development against covid-19.

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