JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1758790

Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations

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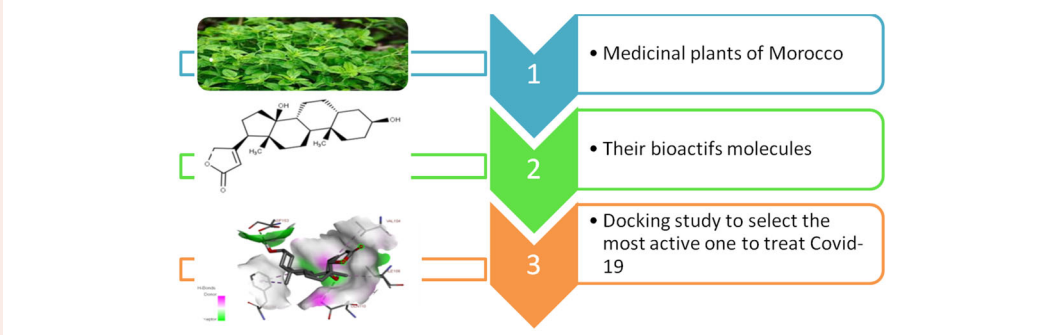
Communicated by Ramaswamy H. Sarma

ABSTRACT

The new Corona-virus, recently called the severe acute respiratory syndrome Coronavirus (SARS-CoV-2) appears for the first time in China and more precisely in Wuhan (December 2019). This disease can be fatal. Seniors, and people with other medical conditions (diabetes, heart disease…), may be more vulnerable and become seriously ill. This is why research into drugs to treat this infection remains essential in several research laboratories. Natural herbal remedies have long been the main, if not the only, remedy in the oral tradition for treating illnesses. Modern medicine has known its success thanks to traditional medicine, the effectiveness of which derives from medicinal plants. The objective of this study is to determine if the components of natural origin have an anti-viral effect and which can prevent humans from infection by this coronavirus using the most reliable method is molecular docking, which used to find the interaction between studied molecules and the protein, in our case we based on the inhibitor of Coronavirus (nCoV-2019) main protease. The results of molecular docking showed that among 67 molecules of natural origin, three molecules (Crocin, Digitoxigenin, and β-Eudesmol) are proposed as inhibitors against the coronavirus based on the energy types of interaction between these molecules and studied protein.



HIGHLIGHTS

- Determine natural compounds that can have an anti-viral effect and which can prevent humans from infection by this coronavirus;
- Molecular docking to find interaction between the molecules studied and the receptor of COVID-19;
- The synthesis of these molecules and the evaluation of their *in vitro* activity against SARS-Cov-2 could be interesting.

ARTICLE HISTORY
Received 10 April 2020
Accepted 16 April 2020

KEYWORDS
Molecular docking; CoV-2019; natural herbal; crocin; digitoxigenin; β-eudesmol

Introduction

Coronaviruses are non-segmented positive-sense RNA viruses which are part of the family Coronaviridae distributed in humans (Richman et al., 2016), and the subfamily Orthocoronaviridae, there are four genera of coronaviruses; Betacoronavirus, Alpha coronavirus, Gamma coronavirus and Deltacorona virus (Schwartz & Graham, 2020).

In humans, especially common colds affecting children and adults, are called mild illnesses. However, there are two zoonotic coronaviruses which are cited: The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) which can especially affect the respiratory system through serious infections. In addition, the latter have the same characteristics:

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Table 1. Chemical Composition and Percentages of several plants.

N° Compound	Name	Plant	%
1	Estragol	Foeniculum Vulgare	5.29
2	β-Phellandren	Nerium Oleander	4.84
3	β-Eudesmol	Lauris Nobilis L	2.39
4	Amorphan	Nerium Oleander	8.11
5	α-Terpinyl acetate	Lauris Nobilis L	10.49
6	α-Terpeneol	Myrtus Communis L	3.84
		Lauris Nobilis L	9.68
7	Myrtenyl Acetat	Myrtus Communis L	25.05
		Lavandula Stoechas	11.54
8	β-Thujone	Sauge Officinal	3-8.5
9	Camphre	Sauge Officinal	4.5-24.5
10	α-Thujone	Sauge Officinal	18-43
11	Isoamyl-2-methyl butyrate	Ammi Visnaga L	27.68
12	Cis- linalool oxide	Ammi Visnaga L	2.14
13	α-Terpinene	Ammi Visnaga L	3.97
14	Amyl valerate	Ammi Visnaga L	9.98
15	Amyl isobutyrate	Ammi Visnaga L	16.04
16	Allyl-methyl disulfide	Allium Sativum	1.71
		Thymelea Tartonraira	2.96
		Artemisia Vulgaris	2.58
17	Limonene	Foeniculum Vulgare	8.14
		Nerium Oleander	5.01
18	Diallyl sulfide	Allium Sativum	0.66
19	Diallyl disulfide	Allium Sativum	14.30
20	Diallyl trisulfide	Allium Sativum	46.52
21	Tricyclene	Thymelea Tartonraira	7.11
		Thymelea Tartonraira	3.1
22	β-Carophyllene	Eugenia Caryophyllus	5-14
		Thymelea Tartonraira	37.92
23	D-Camphor	Lavandula Stoechas	3.47
		Artemisia Vulgaris	16.72
24	Camphene	Thymelea Tartonraira	14.66
		Artemisia Vulgaris	8.35
25	Borneol	Thymelea Tartonraira	2.45
		Artemisia Vulgaris	19.65
		Thymelea Tartonraira	10.98
26	α-Pinene	Myrtus Communis L	10
		Nerium Oleander	5.54
		Thymelea Tartonraira	8.39
27	1-8 Cineol	Myrtus Communis L	43.03
		Nerium Oleander	6.58
		Artemisia Vulgaris	3.23
		Eugenia Caryophyllus	80
28	Eugenol	Lauris Nobilis L	2.15
29	Acetyleugenol	Eugenia Caryophyllus	6.6
	Terpine-4-ol	Nerium Oleander	3.98
30		Lauris Nobilis L	2.39
	Sabinene	Nerium Oleander	3.22
31		Lauris Nobilis L	3.15
32	Pulegone	Mentha Rotundifolia	85.47
33	Methyl-Eugenol	Lauris Nobilis L	4.10
34	Linalool	Artemisia Vulgaris	6.77
		Lauris Nobilis L	8.78
		Ammi Visnaga L	22.71
35	Fenchone	Foeniculum Vulgare	9.55
		Lavandula Stoechas	6.94
36	Eucalyptol	Lauris Nobilis L	30.52
37	Trans-Cinnamylacetat	Cinnamomum Cassia	4.69
38	Trans-Cinnamaldehyde	Cinnamomum Cassia	90.08
39	Undecan	Allium Cepa L	8.09
40	Undecane-2-6-dimethyl	Allium Cepa L	6.86
41	2-carboxylic acid,3- methyl thiophene	Allium Cepa L	8.96
42	Safranal	Crocus Sativus L	n.d
43	pi-Cymene	Thymus Broussoneti	11
44	Picrocrocin	Crocus Sativus L	n.d
45	Neriine	Nerium Oleander	22.56
46	ɤ -Terpinene	Thymus Broussoneti	8.99
47	Dodecan	Allium Cepa L	28.69
48	Digitoxigenine	Nerium Oleander	11.25
49	Crocin	Crocus Sativus L	N.D
50	Crocetin	Crocus Sativus L	N.D
51	Calarene	Nerium Oleander	5.12
52	1,2,4-Trithiolane,3,5-dimethyl	Allium Cepa L	5.82

(*continued*)

Table 1. Continued.

N° Compound	Name	Plant	%
53	Trans-Anethole	Foeniculum Vulgare	53.2
54	Undecan,2methyl	Allium Cepa L	3.59
55	6-Isopropenyl-4,8a-Dimethyl-1,2,3,5,6,7,8, 8a-Octahydronaphthalene-2,3-diol	Lavandula Stoechas	4.56
56	α-Terpinene	Myrtus CommunisL	2.90
57	β-Ocimene	Artemisia Vulgaris	2.21
58	Bicyclogermacrene	Artemisia Vulgaris	3.18
59	Acetat Bornyl	Lavandula Stoechas	8.86
60	Cubenol	Lavandula Stoechas	2.55
61	D-Fenchol	Lavandula Stoechas	6.62
62	Geranyl Acetat	Myrtus CommunisL	2.85
63	Germacrene D	Artemisia Vulgaris	3.82
64	2-Methyl-9-(prop-1-en-3-ol-2-yl)Bicyclo[4.4.0] dec-2-en-4-ol	Lavandula Stoechas	4.50
65	Mycrene	Artemisia Vulgaris	3.8
66	Thymol	Thymus Broussoneti	63.09
67	Viridifloral	Lavandula Stoechas	6.10

production factors, nosocomial transmission, replication in the lower respiratory tract and viral immunopathology. MERS-CoV and SARS-CoV result from serious public health problems which ultimately lead to epidemics resulting in significant loss of life (Hui, 2017; Perlman, 2020; Hui & Zumla, 2019). When these two zoonotic coronaviruses infect pregnant women, they can lead to poor obstetric outcomes, including maternal morbidity and death. There is currently no specific vaccine or treatment approved for coronavirus infection (Hui & Zumla, 2019; Song et al., 2019).

In late December 2019, an outbreak of a new disease, the coronavirus (COVID-19; previously known as 2019-nCoV) (Wu et al., 2020; Huang et al., 2020), was reported in Wuhan, the capital from Hubei province and a large city of around 11 million people in the central region of the People's Republic of China (Zhu, 2020), which subsequently affected 26 countries around the world. China immediately declared the epidemic to the World Health Organization (WHO) and also shared the sequence information with the international community after the discovery of the causative agent. WHO has done its part by coordinating the development of the diagnosis; issue guidelines for patient monitoring, sample collection and treatment; and provide up-to-date information on the epidemic (Munster et al., 2020). To date, the primary source of infection has been pneumonia patients infected with COVID-19. Transmission of respiratory droplets is the main route of transmission, which can also be transmitted by contact (G. O. of N. H. Committee & Office of State Administration of Traditional Chinese Medicine, 2020). The source of the virus and its ability to spread between people remains unknown, with an increasing number of cases showing signs of human-to-human transmission (Zhu, 2020; Chan et al., 2020).

Currently, there are still no effective treatments that target the coronavirus and the development of these treatments requires months and years, so we must be oriented towards treatments of natural origin based on aromatic and medicinal plants to have the compounds having the ability to inhibit COVID-19 (Chen & Nakamura, 2004). The appearance of SARS, pushes a category of researchers to find anti-coronavirus agents, including certain natural compounds that exist in Morocco herbal medicines.

In our study we made a selection of plants based on two principles: the first one is oral efficacy, this means that the majority of Moroccan plants should be absorbable by the oral route, the second one is the compatibility of traditional use, then we have used molecular docking study to selected potential compounds that could have an anti-coronavirus effect by fighting their energy and type of interactions in studied enzyme.

2. Materials and methods

2.1. Data set

For this study we have selected 67 compounds extracted from different aromatic and medicinal plants, Table 1 shows the origin for each studied compound and the percentage present in each plant. These molecules were considered to molecular docking study.

2.2. Molecular docking

Molecular docking analysis was used to study the binding affinity and the type of interactions between all compounds (67 molecules) and the target (Coronavirus (2019-nCoV) main protease).

The steps for preparing ligands and proteins for docking protocol were done in the Autodock 1.5.4 tools from MGL Tools package employing default settings (Morris et al., 1998), a grid box ($x = -26{,}283$, $y = 12{,}599$, $z = 58{,}965$ at 1 Angstrom spacing), the bioactive conformations were simulated employing Autodock vina (Trott & Olson, 2010). For autodock vina study, an extended PDB format, termed PDBQT, is used for cordonnante files, which includes atomic partial charges and atom types. Torsion angles were calculated to assign the flexible and non-bonded rotation of molecules. The results were subsequently analyzed using Discovery studio 2016 (Pilot, 2016) and PyMol (DeLano, 2002).

The crystal structure of Coronavirus(2019-nCoV) main protease (PDB entry code: **6lu7)** was downloaded from the protein databank (http://www.rcsb.org), and its original ligand and water were eliminated, then all compounds from our

Table 2. Flavor agents docking results.

N° compound	Binding Energy(Kcal/mol)
1	−4.7
2	−4.7
3	−7.1
4	−5.8
5	−5.7
6	−6.1
7	−5.9
8	−5.6
9	−5.8
10	−5.6
11	−4.8
12	−4.4
13	−4.9
14	−4.3
15	−4.3
16	−3.2
17	−4.6
18	−2.9
19	−2.9
20	−3.3
21	−4.6
22	−6.1
23	−4.7
24	−5
25	−4.8
26	−4.8
27	−5.1
28	−5.5
29	−5.5
30	−5
31	−5.1
32	−5.2
33	−5.1
34	−4.4
35	−5.3
36	−5.3
37	−5.4
38	−5.1
39	−3.9
40	−4.5
41	−4.1
42	−5.3
43	−5
44	−6.8
45	−6.9
46	−4.9
47	−3.9
48	−7.2
49	−8.2
50	−6.2
51	−6.1
52	−3.1
53	−4.5
54	−4
55	−6.4
56	−4.9
57	−4.3
58	−6.1
59	−5.5
60	−5.9
61	−5
62	−5.1
63	−5.9
64	−6.1
65	−4.1
66	−4.9
67	−5.8

data set were docked in the active site of the studied protein. The preparation of the PDB file was done using Discovery Studio 2016 (Pilot, 2016).

3. Results and discussion

Totally, we have docked 67 components, Table 2 shows the binding affinity of natural compounds toward main protease, and Table 3 mentioned the 11 top flavor agent docking result based on binding energy.

Table 2 shows the obtained results from the molecular docking study carried out on all the molecules present in different medicinal plants (67 molecules), by giving the interaction energy for each compound, there is a difference in energy between each ligand and nCOV-19 main protease.

By comparing all studied molecules with Chloroquine on the basis of the interaction energy criterion. Knowing that the energy value of interaction of the molecule referred (Chloroquine) is (-6 kcal/mol), 11 molecules which have a good interaction with the studied enzyme are mentioned in Table 2. For example, the Crocin at interaction energy equal to (-8.2 kcal/mol), Digitoxigenin at a value of (-7.2 kcal/mol), and β-Eudesmol at a value of (-7.1 kcal/mol). The 3 D binding mode of these compounds is shown in Figures 1 and 2.

From a biological or pharmacological point of view, these first three molecules which are proposed as inhibitors of Coronavirus main protease are molecules having a significant antiviral power and according to bibliographical research and experiments which have already done, the results found for each molecule of natural origin is as following:

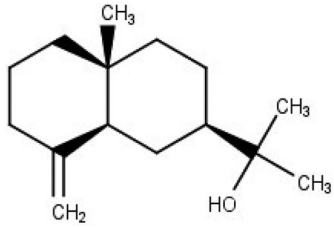
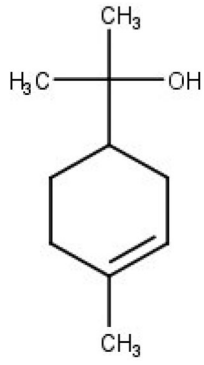
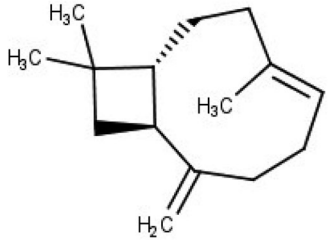
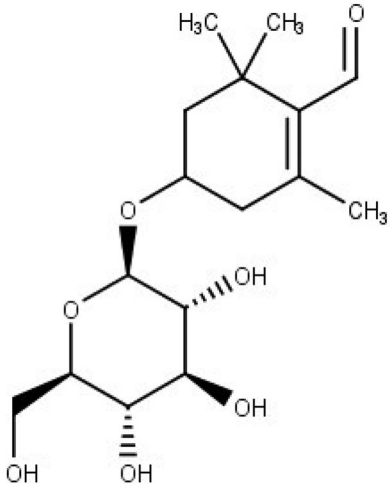
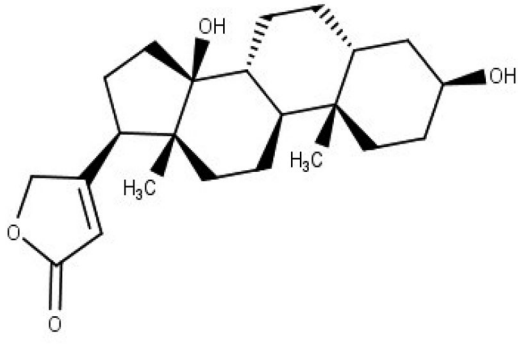
Crocin is an important compound in Crocus Sativus L, it has the capacity to inhibit the replication of HSV before and after the entry of virions in Vero cells. Crocin could be a promising anti-HSV and anti-HIV agent for herbal medicine against viral infections (Soleymani et al., 2018).

Digitoxigenin: represents 11.25% of the quantity present in Nerium Oleander, the derivatives of these molecules are used as antiviral and anti-cancer inhibitors (Boff et al., 2019).

β–Eudesmol despite its low amount of Lauris Nobilis L which contains only 2.39%, but this compound has a good interaction with the target, and it has significant antibacterial and antiviral power (Astani et al., 2011).

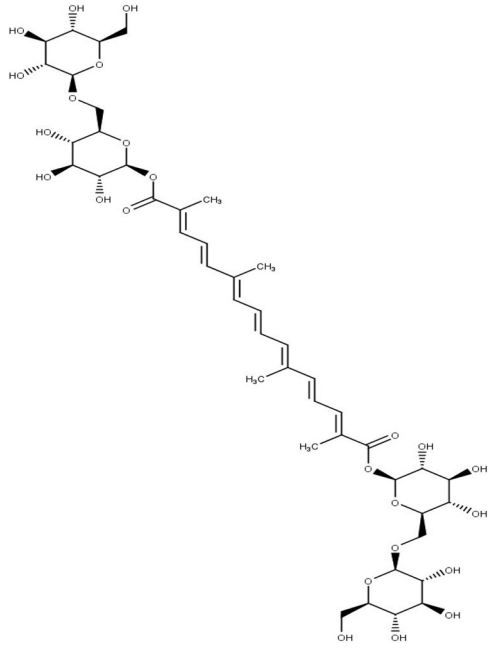
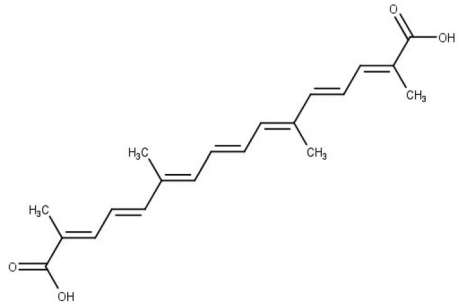
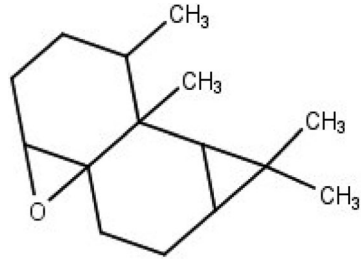
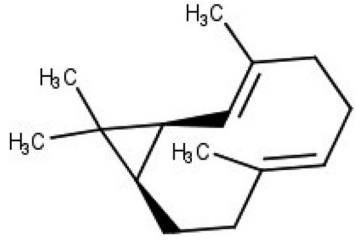
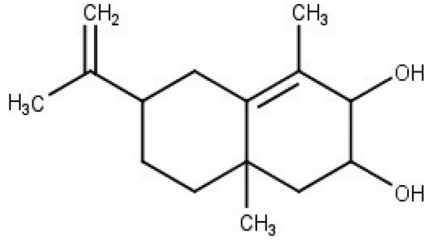
In our study, we took into account the interaction energies, so the interactions of the 1st level concern the hydrogen bonds, those of the 2nd level concerning the interactions between π systems and cation -π interactions, while the interactions of the 3rd level are hydrophobic contacts and non-specific Van der Waals interactions between aliphatic or aromatic carbon atoms. These interactions are generally spherical with a radius of 4 Å and cover most of the ligand. So, for the displacement of ligand in the binding site of our enzyme, the first level of interactions was considerate as the most important, the presence of Hydrogen bond interaction in selected complex explains that we have a good interaction between the three molecules and the studied protein (Table 4, Figure 3 and 4) (Adnan, 2019).

Table 3. 11Top compounds docking results.

N°	Name	Structure	Binding Energy
3	β-Eudesmol		−7.1
6	α-Terpeneol		−6.1
22	β-Carophyllene		−6.1
44	Picrocrocin		−6.8
48	Digitoxigenine		−7.2

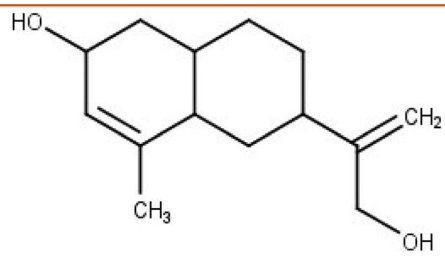
(*continued*)

Table 3. Continued.

N°	Name	Structure	Binding Energy
49	Crocin		−8.2
50	Crocetin		−6.2
51	Calarene		−6.1
55	Bicyclogermacrene		−6.1
58	6-Isopropenyl-4,8a-Dimethyl-1,2,3,5,6,7,8,8a-Octahydronaphthalene-2,3-diol		−6.4

(*continued*)

Table 3. Continued.

N°	Name	Structure	Binding Energy
64	2-Methyl-9-(prop-1-en-3-ol-2-yl)Bicyclo[4.4.0] dec-2-en-4-ol		−6.1

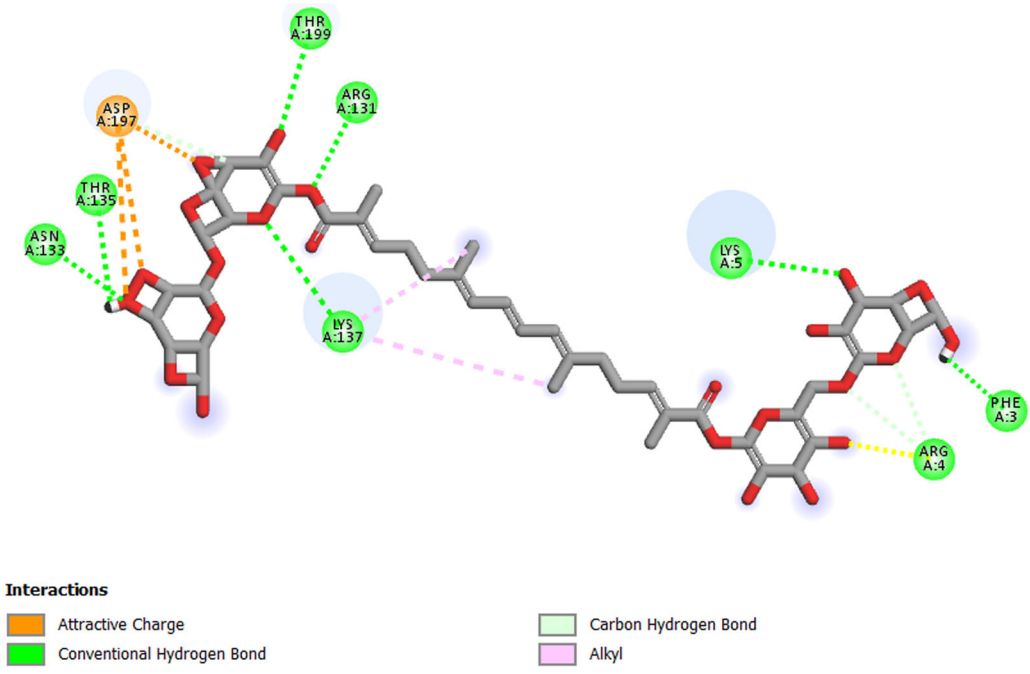


Figure 1. 2 D View of the binding conformation of the Crocin inhibitor at the active site of Coronavirus (2019-nCoV) main protease.

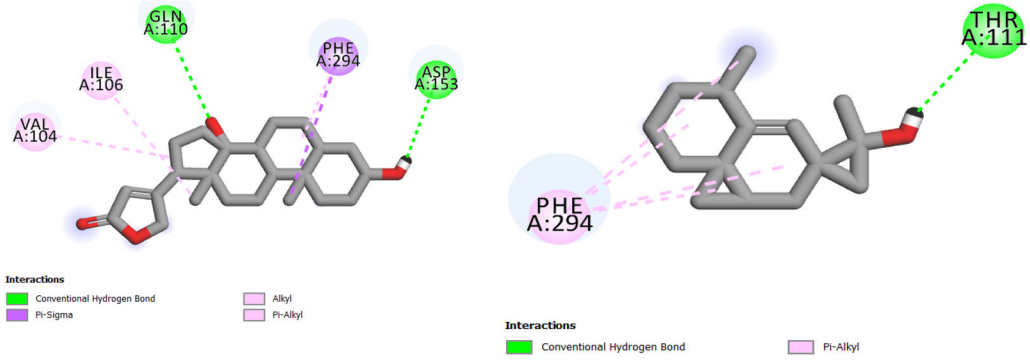


Figure 2. 2 D View of the binding conformation of the Digitoxigenin and β–Eudesmol inhibitors at the active site of Coronavirus (2019-nCoV) main protease.

4. Conclusion

Today, the search for new molecules with a preservative power of natural origin is based on ethnobotanical studies which make it possible to carry out inventories of plants in a zone or a country, then on phytochemical and pharmacological studies and well other scientific aspects, so, the importance of the use of these medicinal plants which pushed us to seek and find the molecules which can prevent SARS-CoV-2 infection. Based on molecular docking,

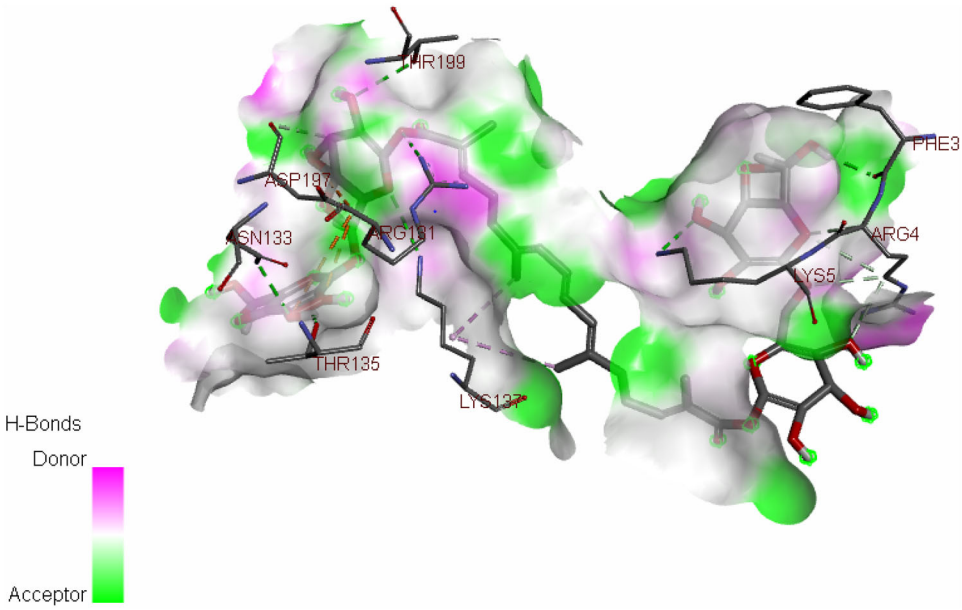


Figure 3. 3 D View of the binding conformation of the Crocin inhibitor at the active site of Coronavirus (2019-nCoV) main protease (Hydrogen Bond interaction).

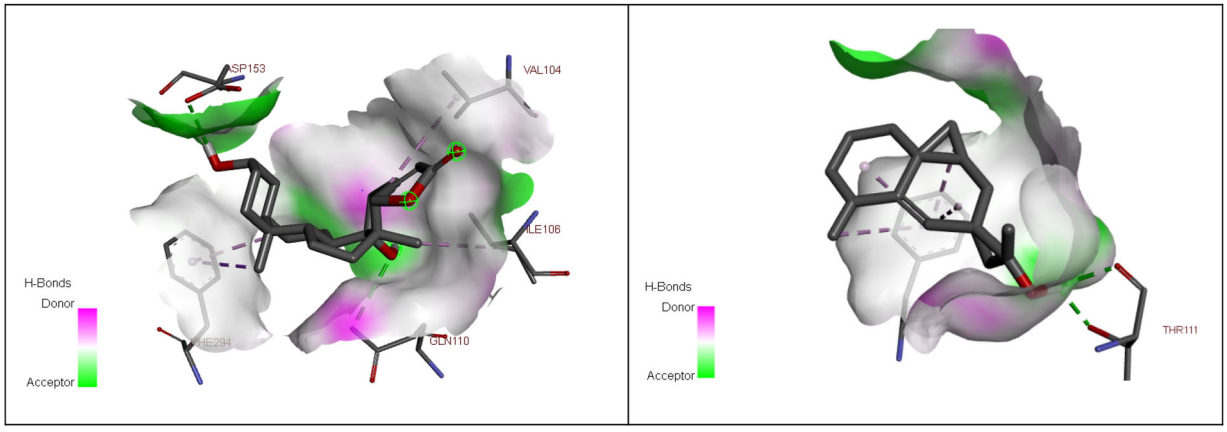


Figure 4. 3 D View of the binding conformation of the Digitoxigenin and β–Eudesmol inhibitor at the active site of Coronavirus (2019-nCoV) main protease (Hydrogen Bond interaction).

Table 4. Hydrogen bond interaction between the three natural compounds and Coronavirus (2019-nCoV) main protease.

Molecules	Residue formed Hydrogen bond interaction with studied compounds
β–Eudesmol	THR 111
Digitoxigenin	GLN 110, ASP 135
Crocin	THR 135, ASN 133, THR 199, LYS 137, LYS 5, PHE 3, ARG 4, ARG 131

the results is very satisfactory, we have found three molecules among 67 which are very interesting either on the chemical side or on the biological side and therefore we propose these three molecules as inhibitor of SARS-CoV-2 main protease. The synthesis of the these molecules and the evaluation of their *in vitro* and *in vivo* activity against SARS-Cov-2 main protease could be interesting, before clinical essay.

Acknowledgements

We are grateful to the "Association Marocaine des Chimistes Théoriciens" (AMCT) for its pertinent help concerning the programs.

Disclosure statement

The authors declare that they have no competing interests.

References

Adnan, A. (2019). Nouvelles molécules organiques bioactives liées à l'inhibition des kinases. Utilisation Des Méthodes QSAR-3D, Docking Moléculaire et ADMET. Chimie Physique et Modélisation, Meknès, Université Moulay Ismail.

Astani, A., Reichling, J., & Schnitzler, P. (2011). Screening for antiviral activities of isolated compounds from essential oils. *Evidence*-Based Complementary and Alternative Medicine, *2011*, 1–8. . https://doi.org/10.1093/ecam/nep187

Boff, L., Munkert, J., Ottoni, F. M., Zanchett Schneider, N. F., Ramos, G. S., Kreis, W., Fernandes de Andrade, S., Dias de Souza Filho, J., Braga, F. C., Alves, R. J., Maia de Pádua, R., & Oliveira Simões, C. M. (2019). Potential anti-herpes and cytotoxic action of novel semisynthetic digitoxigenin-derivatives. *European* Journal of Medicinal Chemistry., *167*, 546–561. https://doi.org/10.1016/j.ejmech.2019.01.076

Chan, J. F.-W., Yuan, S., Kok, K.-H., To, K. K.-W., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C. C.-Y., Poon, R. W.-S., Tsoi, H.-W., Lo, S. K.-F., Chan, K.-H., Poon, V. K.-M., Chan, W.-M., Ip, J. D., Cai, J.-P., Cheng, V. C.-C., Chen,

H., Hui, C. K.-M., & Yuen, K.-Y. (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *The Lancet*, *395*(10223), 514–523. https://doi.org/10.1016/S0140-6736(20)30154-9

Chen, Z., & Nakamura, T. (2004). Statistical evidence for the usefulness of Chinese medicine in the treatment of SARS. *Phytotherapy Research*, *18*(7), 592–594. https://doi.org/10.1002/ptr.1485

DeLano, W. L. (2002). Pymol: An open-source molecular graphics tool. *CCP4 Newsl. Protein Crystallogr*, *40*(1), 82–92.

G. O. of N. H. Committee, Office of State Administration of Traditional Chinese Medicine (2020). Notice on the issuance of a programme for the diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (Trial Version 4). 2020.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *The Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Hui, D. S. (2017). Epidemic and Emerging coronaviruses (severe acute respiratory syndrome and middle east respiratory syndrome. *Clinics in Chest Medicine*, *38*(1), 71–86. https://doi.org/10.1016/j.ccm.2016.11.007

Hui, D. S., & Zumla, A. (2019). Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. *Infectious* Disease Clinics of *North* America, *33*(4), 869–889. https://doi.org/10.1016/j.idc.2019.07.001

Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K., & Olson, A. J. (1998). Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *Journal of Computational Chemistry*, *19*(14), 1639–1662. https://doi.org/10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B

Munster, V. J., Koopmans, M., van Doremalen, N., van Riel, D., & de Wit, E. (2020). A novel coronavirus emerging in China—key questions for impact assessment. *New England Journal of Medicine*, *382*(8), 692–694. https://doi.org/10.1056/NEJMp2000929

Perlman, S. (2020). Another decade, another coronavirus. *Massachusetts Medical Society*, *382*, 760–762. https://doi.org/10.1056/NEJMe2001126

Pilot, P. (2016). Dassault Systèmes BIOVIA, discovery studio modelling environment. Release.

Richman, D. D., Whitley, R. J., & Hayden, F. G. (2016). *Clinical Virology*. John Wiley & Sons.

Schwartz, D. A., Graham A. L. (2020). Potential maternal and infant outcomes from coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: Lessons from SARS, MERS, and other human coronavirus infections. *Viruses*, *12*(2), 194. https://www.mdpi.com/1999-4915/12/2/194

Soleymani, S., Zabihollahi, R., Shahbazi, S., & Bolhassani, A. (2018). Antiviral effects of saffron and its major ingredients. *Current Drug Delivery*, *15*(5), 698–704. https://doi.org/10.2174/1567201814666171129210654

Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., Zhu, H., Zhao, W., Han, Y., & Qin, C. (2019). From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses*, *11*(1), 59. https://doi.org/10.3390/v11010059

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*, *31*(2), 455–461. https://doi.org/10.1002/jcc.21334

Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Song, Z.-G., Hu, Y., Tao, Z.-W., Tian, J.-H., Pei, Y.-Y., Yuan, M.-L., Zhang, Y.-L., Dai, F.-H., Liu, Y., Wang, Q.-M., Zheng, J.-J., Xu, L., Holmes, E. C., & Zhang, Y.-Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

Zhu, N. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of* Medicine, 382, 727–733. https://doi.org/10.1056/NEJMoa2001017