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SARS-CoV-2 Main Protease inhibitors in trace constituents from Algerian herbal medicines using *in silico* approaches

B. Yabrir[1*], A. Belhassan[2], T. Lakhlifi[2], G.S. Moran[3], M. Bouachrine[2], L.G. Candia[4]

[1] University Ziane Achour, Djelfa,
Cité 05 Juillet Route Moudjbara, BP:3117 Djelfa, 17000, Algeria
[2] Moulay Ismail University of Meknes,
2 Marjane, BP:298 Meknes, Morocco
[3] Universidad de Concepcion, Concepcion,
219 Edmundo Larenas, Concepción, Bío Bío, Chile, 4070409
[4] Universidad Católica de la Santísima Concepción, Concepción,
2850 Alonso de Ribera Ave., Concepción, Chile

E-mail: byabrir@yahoo.fr

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Since antiquity, essential oils are considered as a source of bioactive molecules. Some of them have been shown to possess antiviral activities against various virus strains, among them SARS-CoV-2.

The aim of this study is the search for compounds, among minor components extracted from different aromatic and medicinal plants collected from Algerian pharmacopeia, which may posses possible COVID-19 antiviral activities, by molecular docking in the active site of SARS-CoV-2 main protease.

Materials and methods. Thus, in this study 66 compounds which are declared at traces amount by authors in the composition of the essential oils, and selected from 9 Algerian medicinal plants were docked in the active site of SARS-CoV-2 main protease as possible inhibitors of SARS-CoV-2.

Results. The obtained result shows that only Cembrene constitutes the structure with the best affinity in the binding site of the enzyme with a Bioavailability Score "ABS" equal to 0.55 which confirm non Lipinski violations. However, the compound is predicted not orally bioavailable, because too lipophilic (lipophilicity: Log $P_{o/w}$ (XLOGP3)=6.04>+5.0) and less polar (polarity: TPSA=0.00Å²<20 Å²), and it is also predicted as not absorbed, not brain penetrant and not subject to active efflux from the CNS or to the gastrointestinal lumen.

Conclusion. This result deserves to be more detailed and either confirmed or invalidated with a view to better and rational exploitation.

Keywords: cembrene; pharmacokinetic; COVID-19; bioavailability score; Algerian medicine; molecular docking

Abbreviations: ABS — Abbot Bioavailability Score; ACE-2 — Angiotensin-Converting Enzyme 2; ADME — Absorption, Distribution, Metabolism, Excretion; ADMET — Absorption, Distribution, Metabolism, Excretion, Toxicity, Ala — Alanine; AMES — Assay of the ability of a chemical compound to induce mutations in DNA, Asn — Asparagine; BBB — Blood–Brain Barrier; Caco-2 — Colon Cancer Cell Line; CLogP — Octanol/Water Partition Coefficient; CLpro-3 — Enzyme 3-Chymotrypsin-Like protease; CNS — Central Nervous System; COVID-19 — Coronavirus Disease-19; CYP — Cytochrome; CYS — Cysteine; EOs — essential oils; Gln — Glutamine; Glu — Glutamic acid; Gly — Glycine; HB — Hemoglobin; hERG — human Ether-à-go-go-Related Gene; HIA — Human Intestinal Absorption; HIS — Histidine; HSV-1 — Herpes Simplex Virus type 1; Leu — Leucine; MDCK — Madin-Darby Canine Kidney; Met — Methionine; MlogP — Moriguchi logP; MW — Molecular Weight; MWT — Molecular Weight; OCT — Octanol; pdb code 6LU7 — Protein Data Bank (crystal structure of COVID-19 main protease); Phe — Phénylalanine; PkCSM — Predicting small-molecule pharmacokinetic and toxicity properties; PLpro — Papain Like protease; PGP — Permeability-GlycoProtein; Pi-sigma — sigma (σ) and pi (π) bonds; Pro — Protein; PSA — Polar Surface Area; RdRp — RNA-dependent RNA polymerase; QSAR — Quantitative Structure Activity Relationships , RNA — Ribonucleic Acid; SARS-CoV-2 — Severe Acute Respiratory Syndrome Coronavirus 2; Thr — Threonine; TPSA — Total Polar Surface Area; VDss — volume of distribution; WLOGP — Wildman-Crippen LogP (Water Partition Coefficient (logP)); XLOGP3 — Octanol-Water Partition Coefficient (logP).

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Определение ингибиторов основной протеазы SARS-CoV-2 в следовых количествах компонентов алжирских растительных лекарственных средств с использованием методов *in silico*

Б. Ябрир[1], А. Белхассан[2], Т. Лакхлифи[2], Г.С. Моран[3], М. Буахрин[2], Л.Г. Кандия[4]

[1] Зиана Ачур Университет Джельфы,
Алжир, 17000, BP:3117 Djelfa, Cité 05 Juillet Route Moudjbara
[2] Университет Мулая Исмаила в Мекнес,
Марокко, BP:298 Мекнес, Марджана, 2
[3] Университет Консепсьона,
4070409, Чили, Консепсьон, Edmundo Larenas, 219
[4] Католический университет Святейшего Зачатия,
Чили, Консепсьон, пр-кт Alonso de Ribera, 2850

E-mail: byabrir@yahoo.fr

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С древних времен эфирные масла считались источником биологически активных соединений. Было доказано, что некоторые из них обладают противовирусной активностью в отношении различных штаммов вирусов, в том числе SARS-CoV-2.

Целью данного исследования стал поиск соединений среди второстепенных компонентов, выделенных из различных ароматических и лекарственных растений, которые могут обладать возможной противовирусной активностью против COVID-19 путем молекулярного докинга в активном центре основной протеазы SARS-CoV-2.

Материалы и методы. Авторами исследованы 66 соединений, содержащихся в следовых количествах в составе эфирных масел. Соединения получены из 9 лекарственных растений, произрастающих на территории Алжира. Исследуемые соединения были включены в активный центр основной протеазы SARS-CoV-2 в качестве возможных ингибиторов SARS-CoV-2.

Результаты. Полученные результаты показывают, что только чембрен представляет собой структуру с наилучшей аффинностью в сайте связывания фермента с показателем биодоступности, равным 0,55, что подтверждает отсутствие нарушений правила Липински. Однако прогнозируется, что соединение не будет обладать биодоступностью при пероральном приёме, в связи с избыточной липофильностью (липофильность: Log $P_{o/w}$ (XLOGP3)=6,04>+5,0) и низкой полярностью (полярность: TPSA=0.00Å²<20 Å²). Также следует отметить, что чембрен не всасывается, не проникает в мозг и не подвергается активному оттоку из ЦНС или в просвет ЖКТ.

Заключение. Представленные результаты заслуживают более подробного описания, подтверждения, либо аннулирования с целью более эффективного и рационального использования.

Ключевые слова: чембрен; фармакокинетика; COVID-19; биодоступность; алжирская медицина; молекулярный докинг

Список сокращений: ЛС — лекарственное средство; ЛРП — лекарственный растительный препарат; БАС — биологически активные соединения; ACE-2 — ангиотензинпревращающий фермент 2; ADME — всасывание, распределение, метаболизм, экскреция; ADMET — всасывание, распределение, метаболизм, экскреция, токсичность; Ala — аланин; AMES — анализ способности химического соединения индуцировать мутации в ДНК, Asn — аспарагин; ГЭБ — гематоэнцефалический барьер; Caco-2 — линия клеток рака толстой кишки; ClogP — коэффициент разделения октанола и воды; CLpro-3 — фермент 3-химотрипсиноподобная протеаза; ЦНС — центральная нервная система; CYP — цитохром; CYS — цистеин; ЭМ — эфирные масла; Gln — глютамин; Glu — глутаминовая кислота; Gly — глицин; Hb — гемоглобин; hERG — ген специфических калиевых каналов сердца; HIS — гистидин; HSV-1 — вирус простого герпеса 1-го типа; Leu — лейцин; MDCK — клетки Мадин-Дарби почки собаки; Met — метионин; MM — молекулярная масса; OCT — октанол; pdb-код 6LU7 — кристаллическая структура основной протеазы COVID-19; Phe — фенилаланин; PkCSM — прогнозирование фармакокинетических и токсических свойств низкомолекулярных соединений; PLpro — папаиноподобная протеаза; PGP — гликопротеин P; ПМПМ — площадь молекулярной полярной поверхности молекул; RdRp — РНК-зависимая РНК-полимераза; QSAR — соотношение количественной структуры и активности; РНК — рибонуклеиновая кислота; Thr — треонин; TPSA — общая площадь полярной поверхности; VDss —объем распределения; WLOGP — коэффициент разделения воды (logP); XLOGP3 — коэффициент разделения октанола и воды (logP).

INTRODUCTION

The SARS-CoV-2 virus, causative agent of the most dangerous pandemic till now, COVID-19, is the seventh coronavirus [1] appeared in less than twenty years. The structure of this virus is greatly established [2], and well described [3]. This emerged pandemic has raised great public health and socioeconomic concern all around the world [4]. As on February 2021, there have been over 100 million cases and more than 2 million deaths reported since the start of the pandemic [5]; which mean that the pandemic spread very quickly and the numerous

routes of virus transmission have been described in the literature [3]. Knowing the mechanisms of virus infection, penetration into the host cell [1, 6], endocytosis then membrane fusion [7], and its replication cycle [8]; several antiviral strategies have been studied and proposed, among other inhibition of entry of SARS-CoV-2 into the host cell [9], Inhibition of the protease of SARS-CoV-2 [10], Inhibition of the synthesis (replication) of viral RNA [1]. These have constituted potential targets, in probable therapeutic treatments of Covid-19, for drug molecules. Based on previous experiences, drugs have been suggested as promising therapies for the treatment; among which and the most studied, we cite, by way of example: Hydroxychloroquine and chloroquine are used to inhibit SARS-CoV-2 binding to the ACE-2 receptor and impedes membrane fusion [4], or to block the replication of enveloped viruses by inhibiting the glycosylation of envelope proteins) [11]; Remdesevir is designed to inhibit viral RdRp, an enzyme that is integral to viral RNA replication. Without viral RNA replication, the virus is unable to multiply and spread to the infected host's other cells and reduces viral load [4]. As protease inhibitors, Lopinavir in combination with ritonavir may inhibit the action of 3CLpro [12], enzyme 3-chymotrypsin-like protease which plays a crucial role in processing the viral RNA, by disrupting the process of viral replication and release from host cells [13]; and others, in the process of testing and experimentation. However, none of these drugs are immune to side effects (unwanted), to contraindications, to precautions, and to drug interactions; in addition, not all researchers agree on the same opinion on the use of these drugs in the treatment of the pandemic, the pros and cons.

For these reasons and for others, the return to nature is required. Thereby, according to some authors [14] herbal medicines and medicinal plant-based natural compounds offer considerable potential for the development of new agents effective against infections currently difficult to treat and provide a rich resource for novel antiviral drug development. For example, some natural medicines have been shown to possess antiviral activities against various virus strains [14]. So, plants have been utilized for the isolation of novel bioactive compounds as they synthesize a vast number of chemical compounds with complex structures. Natural products, either as pure compounds or as standardized plant extracts, provide unlimited opportunities for new antiviral drugs, since their chemical diversity provides unmatched availability [15]. Indeed, over 70% of therapies have a natural origin or were motivated by natural product chemistry [16]. Therefore, León-Méndez et al [17] consider essential oils "EOs" (complex mixtures of odorous and volatile compounds naturally produced by plants as secondary metabolites and stored in special fragile secretory structures, with low molecular weights and diverse chemical structures, and which bears tens to hundreds of varieties of molecules) as a source of bioactive molecules.

Biological properties of EOs are highlighted [17]. The effectiveness of EO has been attributed mainly to the presence of bioactive compounds in their composition [18]. These biological activities are attributed, in some cases, both to major components and to the minor ones present in these oils, but generally the essential oil, in its totality, acted less than the major constituents [19]. According to Pengelly [20], it is often the unique chemical combination rather than a single component that is responsible for any therapeutic activity. Antiviral activity is one of the other biological activities, which was document. Thus, Ma and Yao [21] summarizes the antiviral properties of EOs from different aromatic plants and EO-derived components on different virus and Tariq et al. [22] enumerates the major constituents of Medicinal and aromatic plants along with their antiviral activities. There, many studies reporting antiviral activity of natural products or isolates against human coronavirus strains are summarized by others [23].

The results of several studies concerning the antiviral efficacy of essential oils from a wide range of plant species led Ma and Yao [21] to draw the following conclusions, for each study: for a study, antiviral efficacy of the EO could be ascribed to its principle; for another, component minor components may be more bioactive than the primary component; among others, either minor or primary are responsible for EO bioactivity; others studies suggest that individual terpene in EO may not contribute equally to the antiviral efficacy of the EO mixture; and concluded that the antiviral effectiveness of EOs can be contributed unequally to the active components, either minor or principle ones, and underlying synergism. It is necessary to point out that to search for potential and specific inhibitors of Coronavirus, the virtual screening is mostly carried out to identify novel phytochemicals against SARS-CoV-2 from different plants. In addition, Wani et al. [24] noted

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that the data available on anti-COVID-19 activity of essential oils is mostly based on in vitro studies and computer aided docking techniques. In this way, four proteins (spike proteins, RdRp "RNA-dependent RNA polymerase", 3CLpro "chymotrypsin-like protease", and PLpro "papain like protease") which are essential for the pathogenicity of virus [14] constitute the molecular targets of natural products against coronavirus [23]. As an example, spike protein was selected for virtual screening [25], main protease [26], PLpro [27], RdRp [28], and 3CLpro [27] all most In Silico screening. Moreover, it has been shown that enveloped viruses respond sensitively to essential oils [15].

Thus, in continuation with our previous works [29], about minor components, extracted from different aromatic and medicinal plants collected from Algerian pharmacopeia, which were docked in the active site of SARS-CoV-2 main protease as possible inhibitors of SARS-CoV-2, so we consequently docked another minor's one, declared as in trace amount by authors, to main protease to look for possible CoVid-19 antiviral agents.

THE AIM of this study is the search for compounds, among minor components extracted from different aromatic and medicinal plants collected from Algerian pharmacopeia, which may posses possible COVID-19 antiviral activities, by molecular docking in the active site of SARS-CoV-2 main protease.

MATERIALS AND METHODS

Data collection

66 compounds were selected from nine medicinal plants growing wild in Algeria namely, *Artemisia arborescens* L. (1 compound), *Pinus halepensis* Mill. (4 compounds), *Eucalyptus* spp. (1), *Juniperus oxycedrus* L. (16), *Myrtus communis* (4), *Ocimum basilicum* (1), *Ocimum gratissimum* (2), *Thymus munbyanus* (28), *Teucrium polium* (10). On the one hand, all these plants are known, in the traditional Algerian pharmacopoeia, to treat pulmonary diseases and in general diseases of the respiratory system. On the other hand, compounds selected were those which are declared at traces amount by authors in the composition of the essential oils of these plants.

Molecular Docking

We performed a docking of studied compounds in the binding pocket of SARS-CoV-2 main protease (pdb code 6LU7) [30], to determine binding affinity and study the intermolecular interactions of studied molecules in the specific target. Molecular docking was implemented by means of the AutoDock program. Autodock vina was used for docking of ligand [31] and Autodock tools 1.5.6 to analysis the resuls [32]. Discovery Studio 2016 program was used to obtain the binding site of crystallographic structure of SARS-CoV-2 main protease (pdb code 6LU7) [33]. The active site of SARS-CoV-2 main protease (pdb code 6LU7) with coordinates (x=-10.782, y=15.787 and z=71.277) has been determined on the basis of the co-crystallized ligand N3 [34]. The grid box parameters were 20×34×20 xyz points with a grid spacing of 1 Å, the grid box was made keeping active site in the center of the box and cover the folic acid binding site in the enzyme (generated using the co-crystallized ligand (N3) as the center for docking) [34]. To prepare ligand and enzyme, an extended PDB format, termed PDBQT, was used for coordinate files, which includes atomic partial charges and atom types using Autodock tools 1.5.6. Torsion angles were calculated to assign the flexible and non-bonded rotation of molecules. The docked results were visualized and analyzed using the Discovery Studio program [35]; And calculation were performed according Hernández-Santoyo et al. [36].

Lipinski's Rule of five and ADMET Prediction

According Lipinski et al [37], the rule of five predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (MWT) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP >4.15). That rule drug likeness for orally available drugs was calculated by using pkCSM [38] web servers. Molecules violating more than one of these parameters may have problems with bioavailability and a high probability of failure to display drug-likeness [39].

ADMET is another concept that focuses on absorption, distribution, metabolism, excretion (ADME) and toxicity characteristics in safe medicines. So, in silico approaches were used to predict and model the most relevant pharmacokinetic, metabolic and toxicity endpoints, thereby accelerating the drug discovery process [40, 41]. The computational prediction of the pharmacokinetic parameters/properties of isolated compounds was done using pkCSM [38] web servers.

RESULTS AND DISCUSSION

Molecular Docking

Molecular docking was performed to find the poses and possible types of interactions between the 66 studied natural compounds molecules and SARS-CoV-2

Mpro (pdb code 6LU7). The results are presented in Table 1.

The study shows that Cembrene is the best compound with binds with the pocket of SARS-CoV-2 Mpro; which could have more inhibitory potential against SARS-CoV-2 main protease than the other studied compounds. It is one of elements declared at amount trace in the essential oil of *Juniperus oxycedrus* L. Previous study showed another minor compound (Abietatriene), for the same species, which have potential inhibition against SARS-CoV-2 main protease with an estimated free binding energy of -6.4 kcal/mol [29]. The essential oils of this species revealed antiviral activity against SARS-CoV and HSV-1 replication in vitro; the effectiveness was assessed by visually scoring of the virus induced cytopathogenic effect post-infection [42]. Also, it is reported in the literature that this species is used in folk medicine in the treatment of many infectious diseases [43].

"Cembranes" family are the most widely occurring diterpenes in Nature and from which hundreds have been isolated, mainly from three sources tobacco, Caribbean gorgonians, and Pacific soft corals [44]. Cembrene, the first naturally occurring 14 memhered cyclic diterpene hydrocarbons ($C_{20}H_{32}$, Fig. 1) to be characterized, is found in pine oleoresins [45]. According Han et al. [46], the structure of a compound determines its physical and chemical properties as well as the ADMET. A range of biological activities has been reported for cembranes, against tumors, inflammation, as well as microbial and/or viral infections [47–49].

Cembrene seems be to inhibit viral receptor with a docking score of -6.3 kcal/mol through the Alkyl bond with CYS-145 and Pi-sigma HIS-41 (Fig. 2). Such types of bond help to improve the hydrophobic interaction of the ligand in the binding pocket of the receptor [50]. According the same authors, a large number of Pi-sigma interactions, which largely involves charge transfer, helps in intercalating the drug in the binding site of the receptor and, on the other hand, the complex stability can be linked to the with extra Pi-sigma interaction.

Elsewhere, many other types of hydrophobic/hydrophilic interactions were also perceived comprising Van der Waals, Conventional Hydrogen Bonds, Amide-Pi Staked, Carbon Hydrogen Bond, and Alkyl/Pi-Alkyl types. These interactions were shaped between The N3 co-crystallized ligand with Asn142, Glu 166, His 164, Gly 143, Thr 190, Gln 189, His 163, Phe 140, Leu 141, Met 165, His 172, Leu 167, Ala 191, Met 167, Pro 168, Met 49, His 41 amino acids residues in the active site of studied enzyme, SARS-CoV-2 Mpro (-6.9 kcal/mol) [51].

Lipinski's Rule of five and ADMET Prediction

The molecular weight and other parameters for cembrene are shown in table 2. Cembrene was found to be fitting well with the Lipinski rule of 5 for drug likeliness, with one violation concerning Log P, whereas the co-crystallized ligand presented three Lipinski Violations. The n-octanol-water partition coefficients, usually expressed as logP values, are used as a measure of lipophilicity and the importance of the use of these values in quantitative structure activity relationships (QSAR) is well established for prediction of biological or pharmacological activity of compounds [52]. The logP is closely related to the transport properties of drugs and their interaction with receptors [53].

These physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability and comprise the first steps in oral bioavailability [54]. For example, the higher molecular weight compounds are in general less likely to be orally active than lower one; also, rotatable bond count is now a widely used filter following the finding that greater than 10 rotatable bonds correlate with decreased oral bioavailability. In a general way, Oral drugs are lower in MWT and have fewer H-bond donors, acceptors and rotatable bonds [54], which coincides with our result.

The computational prediction of the pharmacokinetic parameters/properties of Cembrene are displayed in Table 3. Pharmacokinetic parameters are derived from the measurement of drug concentrations in blood or plasma [40]. Han et al. [46] attribute each parameter to some factors which depend like that: the absorption of drugs depends on factors including membrane permeability [indicated by colon cancer cell line (Caco-2)], intestinal absorption, skin permeability levels, P-glycoprotein substrate or inhibitor. The distribution of drugs depends on factors that include the blood–brain barrier (logBB), CNS permeability, and the volume of distribution (VDss). Metabolism is predicted based on the CYP models for substrate or inhibition (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). Excretion is predicted based on the total clearance model and renal OCT2 substrate. The toxicity of drugs is predicted based on AMES toxicity, hERG inhibition, hepatotoxicity, and skin sensitization. For more detail, Waterbeemd and Gifford [40] well described and reviewed the key pharmacokinetic parameters and their importance for the dose regimen and dose size.

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Table 1 – Affinity of the best conformation in the binding pocket of SARS-CoV-2 Mpro

Compounds	Score (kcal/mol)	Compounds	Score (kcal/mol)
Methyl eugenol	-4.9	Phellandrene	-4.5
Tricyclene	-4.0	trans-PinoCarveol	-4.5
Terpine*n*-4-ol	-4.7	Neryl acetate	-5.2
α-Terpinyl acetate	-5.2	α-Bisabolol	-5.7
Manoyl oxide	-5.8	Isoamyl 2-methyl butyrate	-4.4
δ-Terpineol	-5.2	*n*-Nonanal	-3.8
d-3-Carene	-4.4	Z-Thujone	-4.5
n-Octanol	-3.6	E-Verbenol	-4.8
n-Nonanal	-3.8	Thuj-3-e*n*-10-al	-4.9
Terpin-1-ol	-4.8	Geraniol	-4.8
Fenchyl acetate	-4.9	Geranial	-4.6
cis-Carveol	-4.6	α-E-Bergamotene	-5.0
trans-Piperitol acetate	-5.0	14-hydroxy-α- Muurolene	-5.5
trans-β-Damascenone	-4.9	β-Bisabolenol	-5.9
β-Calacorene	-5.8	Dibutyl phthalate	-5.6
7-epi-a-Eudesmol	-5.7	α-Terpinolene	-4.9
Juniper camphor	-5.4	4-Terpineol	-4.7
(E,Z)-Farnesol	-5.3	cis-Linalool oxide	-4.7
β-Bisabolenal	-5.8	*n*-Octanol	-3.6
(Z,E)-Farnesyl acetate	-5.6	6,7-Epoxymyrcene	-4.3
(E,E)-Farnesyl acetate	-5.8	*n*-Nonanal	-3.8
Cembrene	**-6.3**	trans-Thujone	-4.9
(3Z)-Hexenol	-3.8	trans-*p*-Mentha-2,8-dien-1-ol	-4.8
n-Hexanol	-3.6	cis-*p*-Mentha-2-en-1-ol	-4.8
3-Octanone	-3.9	cis-Limonene oxide	-4.9
3-Octanol	-3.9	trans-limonene oxide	-4.6
Isoborneol	-4.6	δ-Elemene	-4.9
Trans-pinocamphone	-4.8	*n*-hexadecanoic acid	-4.4
Neral	-4.6	α-trans-Bergamotene	-5.2
p-Vinylguaiacol	-4.8	cis-Muurola-4(14),5-diene	-5.1
Sesquicineole	-5.7	*n*-Heptacosane	-4.1
α-Calacorene	-5.6	*n*-Nonacosane	-4.3
Cyclocolorenone	-5.5	*n*-Dotriacontane	-4.1

Table 2 – Lipinski's rule of potential inhibitor: Cembrene

	Log P	HB Acceptor	HB Donor	Rotatable bonds	MW, g/mol	Lipinski violations
Rule	***<5***	***≤10***	***<5***	***<10***	***≤500***	***≤1***
Cembrene	6.62	0	0	1	272.47	1

Note: HB — hemoglobine; MW — molecular weight.

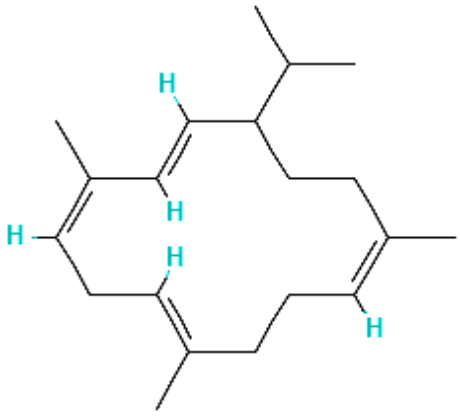

Figure 1 – Structures of Cembrene[1] with the best Affinity in the binding pocket of SARS-CoV-2 Mpro.

[1] Cembrene. PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Cembrene

Table 3 – *In silico* ADMET prediction of potential inhibitor: Cembrene

Property	Model Name	Unit Numeric/Categorical (Yes/No)	Predicted Value
Absorption	Water solubility	log mol/L	-7.207
	Caco2 permeability	log Papp in 10^{-6} cm/s	1.458
	Intestinal absorption (human)	% Absorbed	94.374
	Skin Permeability	log Kp	-1.675
	P-glycoprotein substrate	Yes/No	No
	P-glycoprotein I inhibitor	Yes/No	No
	P-glycoprotein II inhibitor	Yes/No	No
Distribution	VDss (human)	log L/kg	0.667
	Fraction unbound (human)	Fu	0.107
	BBB permeability	log BB	0.689
	CNS permeability	log PS	-2.206
Metabolism	CYP2D6 substrate	Yes/No	No
	CYP3A4 substrate		No
	CYP1A2 inhibitior		No
	CYP2C19 inhibitior		Yes
	CYP2C9 inhibitior		No
	CYP2D6 inhibitior		No
	CYP3A4 inhibitior		No
Excretion	Total Clearance	log ml/min/kg	1.48
	Renal OCT2 substrate	Yes/No	No
Toxicity	AMES toxicity	Yes/No	No
	Max. tolerated dose (human)	log mg/kg/day	0.269
	hERG I inhibitor	Yes/No	No
	hERG II inhibitor	Yes/No	No
	Oral Rat Acute Toxicity (LD50)	mol/kg	1.512
	Oral Rat Chronic Toxicity (LOAEL)	log mg/kg_bw/day	1.244
	Hepatotoxicity	Yes/No	No
	Skin Sensitisation	Yes/No	Yes
	T.Pyriformis toxicity	log µg/L	2.031
	Minnow toxicity	log mM	-0.448

Note: BBB — blood-brain barrier penetration

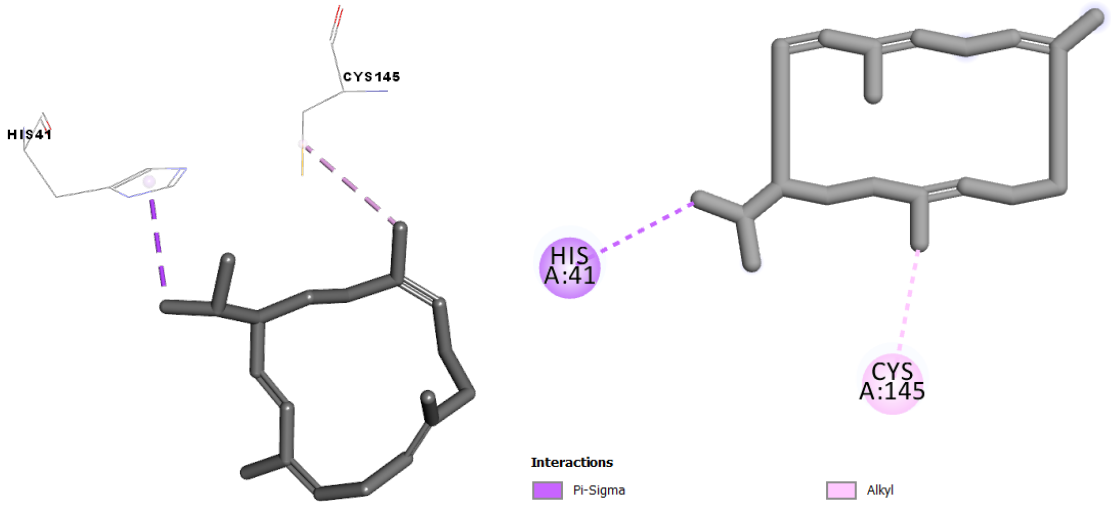

Figure 2 – 2D and 3D presentations of interactions between Cembrene and SARS-CoV-2 Mpro.

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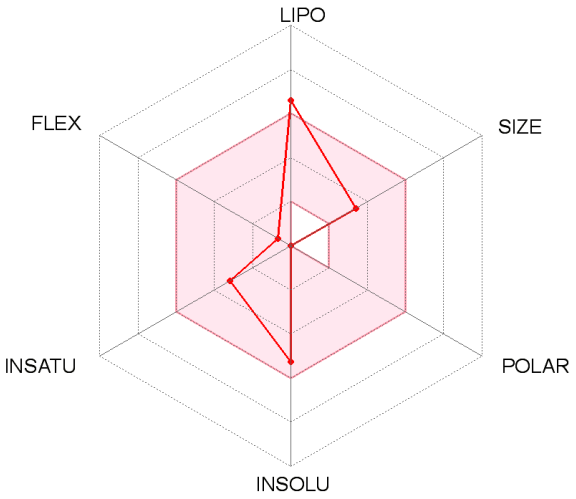

Figure 4 – Bioavailability Radar of Cembrene

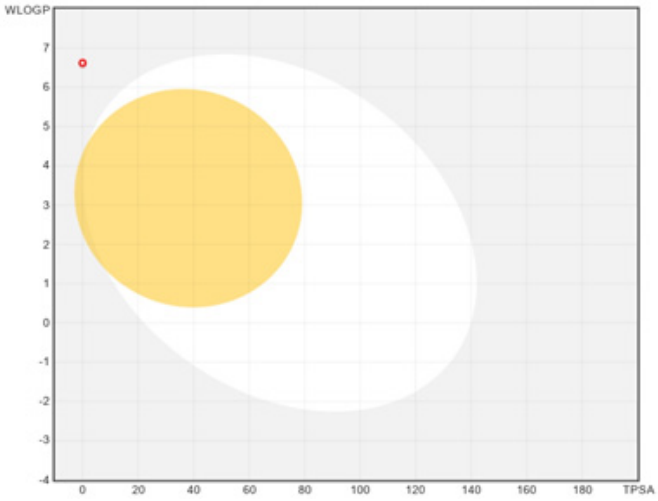

Figure 5 – Boiled-Egg of Cembrene

MWT has a large effect on solubility, our result for solubility (237.281, Moderately soluble) is in agreement with Gleeson [55] for which on average, molecules with MWTs < 300 have solubilities of ≈250 μM (μmol/L), and which is considered as an important component of an orally administered drug, determining the amount freely available to permeate through the gastrointestinal membranes into systemic circulation; also, the increasing of MWT is correlate with decreasing of membrane permeability, according their parameters MDCK or Caco-2.

A Bioavailability Score, ABS identifies poorly- and well-absorbed compounds tested in humans, it is 0.55 for compounds, which pass the rule of five [56]. Our result shows an ABS of Cembrene equal to 0.55 which confirm non Lipinski violations. Considering the bioavailability radar of Cembrene (Fig. 4), the compound is predicted not orally bioavailable, because too lipo (lipophilicity: Log $P_{o/w}$ (XLOGP3)=6.04>+5.0) and less polar (polarity: TPSA=0.00Å²<20 Å²). The molecular polar surface area (PSA) is considered as descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs [57], and lipophilicity as the key physicochemical parameter linking membrane permeability — and hence drug absorption and distribution- with the route of clearance (metabolic or renal) [40]. For instance, it has been reported that target promiscuity as well as toxicity issues like hERG inhibition, phospholipidosis or cytochrome P450 (CYP) inhibitions are more likely to be problematic for compounds with high lipophilicity values; also solubility and metabolism are more likely to be compromised at these high values whereas permeability could be decreased when this property is too low [58].

According Daina and Zoete [59], Gastrointestinal absorption (HIA) and brain penetration (BBB) are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes. So, to this end, the Brain or Intestinal estimated permeation method (BOILED-Egg) is proposed by Daina and Zoete in 2016 [59] as an accurate predictive model that allows for intuitive evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) in function of the position of the molecules in the WLOGP-versus-TPSA referential and which works by computing the lipophilicity and polarity of small molecules. The colored zone is the suitable physicochemical space for orally bioavailability, the white region in the BOILED-Egg graphical is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain and blue dots for P-gp substrates (PGP+) and red dots for P-gp non-substrate (PGP-) as described by the same authors. For this, Cembrene is predicted as not absorbed and not brain penetrant (outside the Egg, Fig. 5) and not subject to active efflux from the CNS or to the gastrointestinal lumen (P-gp non-substrate (PGP-), red dot).

CONCLUSION

A virtual screening technique, including molecular docking, and ADMET Prediction was carried out, for the selection of the compounds which could have a potent antiviral treatment of COVID-19. In total, 66 natural compounds, selected from 9 Algerian herbal medicine, were docked in the active site of SARS-Cov-2 main protease. The results of this study

indicates clearly that, among these compounds, only Cembrene constitutes the structure with the best affinity in the binding site of the enzyme and respect the conditions mentioned in Lipinski's rule, except the Log P, a measure of lipophilicity and closely related to the transport properties of drugs and their interaction with receptors. Concerning the pharmacokinetic properties and bioavailability, Cembrene is predicted not orally bioavailable, because too lipophilic and less polar and. It is also predicted as not absorbed and not brain penetrant and not subject to active efflux from the CNS or to the gastrointestinal lumen. This result might be interest researchers confirm or invalidate the results obtained and push the research thoroughly.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Benalia Yabrir — problem statement, development of the research concept, writing and scientific editing the text of the manuscript; Assia Belhassan — processing the study data, analyzing and describing the results; Tahar Lakhlifi, Mohammed Bouachrine — supervision, editing and manuscript revision; Guillermo Salgado Moran, Lorena Gerli Candia — participation in the development of the study design and article concept.
All the authors confirm their authorship compliance with the ICMJE international criteria (all authors made a significant contribution to the development of the concept, conducting research and preparing the article, read and approved the final version before publication).

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AUTHORS

Benalia Yabrir — Doctor of Sciences (Biology), Professor, Ziane Achour University of Djelfa, Algeria. ORCID ID: 0000-0003-3538-8925. E-mail: byabrir@yahoo.fr; b.yabrir@univ-djelfa.dz

Assia Belhassan — Doctor, Faculty of Sciences, Moulay Ismail University of Meknes, Morocco. ORCID ID: 0000-0002-4447-7308. E-mail: assiabelhassan2013@gmail.com

Tahar Lakhlifi — Full Professor, Laboratory of Molecular Chemistry and Natural Substances, Faculty of Sciences, Moulay Ismail University of Meknes, Morocco. ORCID ID: 0000-0001-6707-9057. E-mail: tahar.lakhlifi@yahoo.fr

Guillermo Salgado Moran — Professor of Chemistry and Science Methodology, Facultad de Ciencias Quimicas. Investigador Extramural, Universidad de Concepcion, Concepcion, Chile. ORCID ID: 0000-0002-5054-989X. E-mail: gsalgado41@gmail.com

Mohammed Bouachrine — Full Professor, Laboratory of Molecular Chemistry and Natural Substances, Faculty of Sciences, Moulay Ismail University of Meknes, Morocco. ORCID ID: 0000-0002-8901-047X. E-mail: m.bouachrine@umi.ac.ma; bouachrine@gmail.com

Lorena Gerli Candia — Doctor of Science, Major in Chemistry, Departamento de Química Ambiental, Facultad de Ciencias, Universidad Católica de la Santísima Concepción, Concepción, Chile. ORCID ID: 0000-0002-1061-2962. E-mail: loregerli@ucsc.cl