

In silico screening of Moroccan medicinal plants with the ability to directly inhibit the novel coronavirus, SARS-CoV-2

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Abstract

In the present study, we investigated natural compounds contained in Moroccan medicinal plants and that might be used as natural inhibitors of the novel coronavirus, SARS-CoV-2, that causes coronavirus disease 2019 (COVID-19). We first performed a literature search for natural inhibitors of SARS or MERS coronaviruses. We then selected natural compounds that have been biologically tested and confirmed to possess anti-coronavirus activity. Subsequently, we used a molecular docking to determine whether the selected molecules could interact with the virus proteins. The compounds selected from virtual screening were then subjected to an *in-silico* analysis of absorption, distribution, metabolism and excretion (ADME) properties to select only natural compounds that could be orally bioavailable. Thereafter, a second search has been launched to select Moroccan medicinal plants that contain at least 3 molecules from those natural compounds. As results, among 41 natural inhibitors of SARS or MERS coronaviruses, only 13 have been successfully passed the ADME filtering. These molecules, showed abilities to interact with the novel coronavirus as it was predicted. Using these molecules and based on the data extracted from literature, 29 Moroccan medicinal plants have been found to contain at least 3 of these coronavirus inhibitors. Therefore, the medicinal plants selected in this study might contain direct anti-SARS-CoV-2 compounds.

Introduction

The current outbreak infection of a novel, highly pathogenic coronavirus SARS-COV-2 (formerly 2019-nCoV) emerged in December 2019 in Wuhan, Hubei Province, China, and which has spread rapidly across the five continents (Zhou et al., 2020). The SARS-COV-2 is a highly virulent human coronavirus with a high fatality rate (Zhou et al., 2020). Human coronaviruses, including the SARS-COV-2 are associated with severe acute respiratory syndrome, and lead to global pandemics with high morbidity and mortality (Hoffmann et al., 2020). Unfortunately, until now, there is no efficient antiviral drug or vaccine for the treatment of COVID-19.

The molecular mechanisms of coronavirus invasion, depends first on cell entry which depends on binding of the viral spike protein (protein S) to cellular receptors of the target cells (Xia et al., 2020). The alveolar epithelial cells, which highly express an angiotensin-converting enzyme 2 (ACE2), recognized by the protein S of the virus, represent an appropriate target for the coronavirus infection in the lung (Hoffmann et al., 2020). After the expression of coronavirus polyproteins, two viral enzymes, which are 3C-Like protease (3CL^{Pro}) also known as main proteinase (M^{Pro}) and the papain-like protease (PL^{Pro}), were reported to be implicated in cleaving the expressed polyproteins into smaller compounds used to produce new viruses (Wrapp et al., 2020). In addition to their essential function for coronavirus replication, they were also reported to inhibit the innate immune responses of the host (Wrapp et al., 2020).

Unfortunately, there are currently no effective drugs targeting COVID-19. In this respect, Anti SARS-CoV-2 drug are urgently needed. Repurposing of existing antiviral drugs (Zhou et al., 2020) or screening of

available databases of natural molecules with antiviral properties is considered a near term strategy that could reduce the time and cost compared to the novo drug discovery.

The functional importance of 3CL^{pro} and PL^{pro} for replication of coronaviruses makes them attractive and promising targets for the development of broad-spectrum of anti-coronavirus drugs (Zhang et al., 2020). As well, spike protein has been also extensively characterized to be a key target for development of antiviral medicines (Letko et al., 2020).

For centuries, medicinal plants have been an invaluable source for drug discovery and development. As a notable illustration, the discovery of artemisinin which was originally isolated from *Artemisia annua* L., is a milestone in the treatment of malaria (Su et al., 2020). As well, numerous medicinal plant compounds have demonstrated antiviral potent towards many viral diseases (Karagöz et al., 2018). Indeed, several natural molecules including kaempferol (Park et al., 2017), gallic acid (Nguyen et al., 2012), procyanidin B1 (Zhuang et al., 2009) and Quercetin (Nguyen et al., 2012) among others, have already been tested *in vitro* to successfully treat SARS and MERS coronaviruses and these compounds could be a potential drug candidate towards SARS-CoV-2. Moreover, currently, different computational studies are moving towards in-silico analyzes to find potential candidates that might be effective for inhibiting the activity of SARS-CoV-2 proteins.

In the present study, we conducted an in-silico drug repurposing by using natural compounds contained in Moroccan medicinal plants in order to identify appropriate natural inhibitors to SARS-CoV-2. For that, molecular Docking was conducted and binding energy was determined against three key targets of the SARS-CoV-2, 3CL^{pro}, PL^{pro} and protein S. Therefore, we further conducted a performed literature analysis to select Moroccan plant species that contain at least three of the selected molecules.

Materials And Methods

Compound selection and ADME screening

Pubmed and Google Scholar papers related to natural inhibitors of SARS or MERS coronaviruses were selected. The query used for this search mode was: “coronavirus AND natural compound AND SARS” or “coronavirus AND natural compound AND MERS”. After analysis of the articles generated by this search, we selected natural compounds biologically tested and confirmed to possess anti-coronavirus activity.

As the main objective of our study is to select natural compounds that could be orally administrated, we ran an in-silico analysis of absorption, distribution, metabolism and excretion (ADME) to select only molecules that could be orally bioactive. For this purpose, we used three indices that are, oral bioavailability (OB), Caco-2 (Caco-2) permeability, and human drug-likeness (DL), using the Traditional Chinese Medicine Systems Pharmacology database (TCMSP). Effectiveness of these three indices was validated by threshold values OB > 30%, Caco-2 > -0.4, and DL > 0.18, respectively (Hu et al., 2019).

Ligand and receptor preparation

Three-dimensional (3D) structures of PL^{pro}, 3CL^{pro}, and protein S of SARS-CoV-2 were retrieved from Protein Data Bank (<http://www.rcsb.org/pdb>) in pdb file formats, corresponding to the PDB ID 6w9c, 6lu7, and 6vyb, respectively. These proteins were served as receptors in docking process. Water molecules and ligands that were still attached to the receptors were removed. Using Autodock Tools (1.5.6), polar hydrogen atoms were added to the receptors. Subsequently, the files were saved in pdbqt file format. The ligands three-dimensional (3D) structures were obtained from the PubChem database (<http://pubchem.ncbi.nlm.nih.gov>). Each ligand's file was downloaded and saved in the sdf file format and converted to pdb using PyMol. Thereafter, AutoDock Tools was used to convert to pdbqt file format.

Molecular Docking

Molecular docking software AutoDock Vina (1.1.2) (Trott et al., 2010) was used to perform protein-compound docking analysis. Using this, the grid box size was set to a dimension (x, y, z) of 50 × 58 × 50, 60 × 70 × 60 and 82 × 98 × 126, and the coordinates (x, y, z) of -11.798, 10.956, 70.020, -26.626, 22.56, 33.809 and 232.215, 189.820, 263.862 for the 3CL^{pro}, PL^{pro} and for the protein S, respectively. Ligands and receptors that have been prepared with the pdbqt file format were copied into the Vina folder and the vina configuration file was typed into notepad, saved with the name 'conf.txt'. Then Vina program was run through command prompt. The results were shown in the output (notepad format) and finally analyzed. All the other vina parameters were kept at their default values.

Plant selection

The medicinal plants selection was conducted in two steps. Based on the results obtained from the ADME screening, only compounds that have been considered to be orally bioactive have been selected. Thereafter, a search has been launched using Pubmed and Google Scholar to select Moroccan medicinal plants that contain at least 3 molecules from those natural compounds.

As an additional step and using the results obtained from above, plants that have been routinely used as either medicinal plants or used in daily diet in Morocco and also contain at least 5 anti-coronavirus compounds have been described for their medicinal value.

Results And Discussion

Natural compounds reported to be anti-SARS or anti-MERS coronavirus and contained in Moroccan medicinal plants

The coronavirus codes for several proteins, some of which are vital for viral entry and replication. The spike protein of coronaviruses facilitates viral entry into the target cells (Hoffmann et al., 2020). In fact, coronavirus cell entry is dependent on the binding of protein S, to a cellular receptor known as ACE2. Two other viral proteins were reported to have essential roles in the replication of the coronavirus. These proteins correspond to the papain type protease (PL^{pro}) and the 3CL type protease (3CL^{pro}) (Hoffmann et

al., 2020). Therefore, these proteins constitute interesting targets for the development of drugs against Sars-Cov-2.

In the present study, we have carried out a multistep screening process to select Moroccan medicinal plants supposed to contain potent natural inhibitors to the SARS-CoV-2, and which could be used as a strategy for the prevention and the treatment of the COVID-19 while, around the world, the virus is still spreading and cause hundreds of deaths every day worldwide (Scheme 1).

Our study was based on two criteria to select the final medicinal plants. First, the selected molecules contained in the screened plants should be orally bioavailable. On the other hand, the selected medicinal plants should contain natural compounds susceptible to act as anti-SARS-CoV-2 possessing ideal oral bioavailability and drug-likeness. To do this, natural compounds proved in previous scientific publications as inhibitors for SARS or MERS coronaviruses have been extracted from PubMed and Google Scholar databases. Subsequently, the obtained molecules have been cross-checked for their existence in Moroccan medicinal plants using a new research on PubMed and Google Scholar. We selected 41 molecules that have been reportedly tested for their antiviral activities with either cell-based experimental systems or enzyme-based system (Table 1).

These molecules were then divided into two groups, one of them contains anti-coronavirus molecules that have been analyzed for their orally absorbable ability using an ADME screening or based on literature. In fact, the anti-viral effects of most of the selected natural molecules have been validated *in vitro* only. Therefore, to meet the requirement that we have installed as first criterion for our study, the molecules should be active through oral preparation. For this, we ran an ADME filtration using three indices, oral bioavailability (OB), Caco-2 (Caco-2) permeability, and human drug-likeness (DL), using the TCMSP database. Among the 41 molecules, only 13 compounds have successfully passed this filtering step (Table 2). The second group is composed of natural compounds that were active against coronavirus but for which the characteristics of oral bioavailability was not available or not appropriate (28 natural compounds). The method developed here is a rapid way to identify natural compounds both contained in Moroccan medicinal plants and also reported to have a high anti-coronavirus activity. The advantage of this approach is that the selected molecules were biologically tested and confirmed for their effectiveness against coronavirus. Furthermore, because of the genetic similarities that exist between SARS or MERS and the new SARS-CoV-2 (Zhou et al., 2020; Park et al., 2016), the selected molecules could have the same efficacy against the novel coronavirus.

We recall here that the selected molecules have been biologically tested against targets from the SARS and MERS coronaviruses, however, the mutations that have been noted between these two viruses and the SARS-CoV-2 could not guarantee the efficiency of the selected natural compounds against the new virus. To overcome this situation, we used molecular docking to determine whether the selected molecules could bind to the 3D structures of the three targets selected for this study (PL^{pro}, 3CL^{pro}, and protein S). In fact, High-resolution crystal structure of the SARS-CoV-2 PL^{pro}, 3CL^{pro}, and protein S have been recently published (Liu et al., 2020; Osipiuk et al., 2020; Walls et al., 2020). The corresponding files

of these structures have been downloaded from the RCSB PDB database. Then, the molecular docking was performed between all the 41 selected molecules and the three targets. Indeed, even if a molecule was reported in the literature to inhibit a specific target of the MERS or SARS coronaviruses, in our study, all selected molecules were docked against the three targets (PL^{PRO}, 3CL^{PRO}, and protein S). The results obtained here are summarized in table 1.

The different molecules were divided into several families of secondary metabolites. From the different classes of molecules, flavonoids were the most reported natural compounds that were tested positive for their anti-coronavirus activities (24/41 molecules). The molecular docking showed that the binding energies of the different molecules ranged between -4.7 and -8.9 Kcal/mol for the PL^{PRO} protein, -5.8 and -9.8 Kcal/mol for the 3CL^{PRO} protein, and -5.3 and -10.4 Kcal/mol for the spike protein. Furthermore, while flavonoids gave the highest vina scores, furocoumarins showed the lowest vina scores for the three targets (Table 1).

Hopefully, from the molecular docking results, our 13 screened compounds showed abilities to bind to the selected proteins of the novel coronavirus as it was predicted. Moreover, most of these molecules showed high binding abilities to more than one protein and suggest a more pronounced effect for those molecules against the SARS-CoV-2 (Molecules in bold Table 1).

Selection of anti-coronavirus herbal plants

The second criterion on which our study was based is the fact that the selected plants should contain 3 or more of the selected anti-coronavirus natural compounds. As explained before, there are just 13 molecules that have passed the test of the oral bioavailability and which were therefore selected for the next step of the study. Using these molecules and based on the data extracted from Pubmed and Google Scholar databases, we selected for this study 29 Moroccan medicinal plants because they meet this criterion (Table 3). However, in the present work, we chose 8 plants that are supposed to be very promising for the prevention and the treatment of the SARS-CoV-2 and we described them in more details. The selected plants have been chosen because they have been routinely used as either medicinal plants or used in daily diet in Morocco and also because they contain at least 5 potential anti-coronavirus compounds. Interestingly, 4 of these plants contain compounds that might inhibit the three targets of the coronavirus (PL^{PRO}, 3CL^{PRO}, and protein S) and which are *Argania spinosa*, *Cydonia oblonga*, *Phoenix dactylifera* and *Punica granatum*. The other plants contain potential inhibitors against either PL^{PRO} and/or 3CL^{PRO}, and which are *Mentha longifolia*, *Salvia officinalis*, *Rosmarinus officinalis* and *Portulaca Oleracea* (Table 3).

Potential Moroccan plants as Sars-CoV-2 PL^{PRO}, 3CL^{PRO}, and protein S inhibitors

Among the 41 natural molecules screened, 13 compounds which possessed the high Oral bioavailability (Table 2), have been reported to exhibit potential anti-coronavirus activity as inhibitors of the proteins PL^{PRO}, 3CL^{PRO}, and protein S. Further, among the 29 Moroccan medicinal plants which were found to

contain 3 to 6 of these molecules, 8 of them are described below as they might contain direct anti-SARS-CoV-2 molecules. These plants are: *Argania spinosa* L., *Cydonia oblonga*, *Phoenix dactylifera*, *Punica granatum*, *Mentha longifolia*, *Salvia officinalis*, *Rosmarinus officinalis* and *Portulaca Oleracea*.

Argania spinosa

Argania spinosa L. or *Argania spinosa* L. Skeels, which contains five potent anti-coronavirus molecules; procyanidin B1, kaempferol, betulinic acid, quercetin and luteolin, is commonly known as argan tree (Table 3). It is an agroforestry species that belongs to the *Sapotaceae* family (Guillaume et al., 2019), and it is an endemic species from south-western Morocco (Hebi et al., 2018) where it covers an area of about 320 000 square miles (Charrouf et al., 2011). This species 'genus *Argania*', is the unique representative of the tropical family *Sapotaceae* growing in the subtropical zone 'Morocco' (Morton et al., 1987).

As a meaningful indigenous alimentary medicine, *A. spinosa* is a valuable potential for Moroccans (El Babili et al., 2010). All the different botanical parts of the *Argania spinosa* like the fruits, wood, leaves, and kernels are exploited for many folk medicine purposes (Khallouki et al., 2017). In fact, the Argan tree based preparations have been considerably used in Morocco for their biological properties for many purposes including among others: diabetes and colopathies (El Babili, et al., 2010), bactericidal and fungicidal remedies, anti-atherosclerotic, hepatoprotective properties, several dermatological indications, rheumatism disease and the treatment of lung infections (Moukal et al., 2004).

A wide array of chemical compounds has been identified and isolated up to now from different parts of the Argan tree (Bonvicini et al., 2017). Abundant studies showing that this tree possesses many secondary metabolites including flavonoids, polyphenols, tannins saponins, alkaloids, quinones, anthraquinones cyanidins, terpenoids, sterols, mucilage, sesquiterpenes, reducing sugars, glucosides, carbohydrates and vitamin E. Thereby, the Argan tree has been subjected to many pharmacological screenings. There is evidence of their wide spectrum of *in vitro*, and *in vivo* biological activities including antioxidant (Koufan et al., 2020), anti-inflammatory (Kamal et al., 2019), antidiabetic (Hebi et al., 2018), antibacterial (Bonvicini et al., 2017), anti-fungal (El Abbassi et al., 2014), anticancer (Khallouki et al., 2017), antiviral (including anti-HIV) (Dzubak et al., 2006) and antimalarial (El Babili et al., 2010) activities.

Cydonia oblonga

Cydonia oblonga chemical composition has been reported the presence of five anti-coronavirus compounds including: procyanidin B1, β -sitosterol, kaempferol, betulinic acid and luteolin (Table 3). *Cydonia oblonga* (*Rosaceae* family) commonly known as quince, is a fruit of a deciduous tree (Silva et al., 2004). Quince is native to Mediterranean region and Central Asia having a long-term history of medicinal and ethnobotanical use. *C. oblonga* is considered as one of the most important medicinal plants throughout the world (Sabir et al., 2005). This is a medicinal plant known from ancient times by their health beneficial properties for curing several diseases such as cancer, hepatitis, diabetes and respiratory infections. Likewise, various parts of quince plant are used to cure respiratory disorders such as asthma, cough, and bronchitis (James et al., 2002).

A large number of studies conducted have reported that quince is a good, safe, low-cost and excellent natural source of different classes of phenolic compounds, such as flavonols and flavone heterosides and caffeoylquinic acids (Márcia et al., 2010). This species possesses various phytoconstituents including quercetin, procyanidin B2, B3 procyanidin, and 9 kaempferol derivatives (Silva et al., 2001). In addition to this, the seed has been reported to be a rich source of fat soluble compounds that include tocopherol (α - β - γ), sitosterol, stigmastrol, vitamin C, organic acids, citric acid, oxalic acid, fumaric acid, free amino acids, and phenolic compounds (Silva et al., 2004). Therefore, *C. oblonga* parts used medicinally were leaves, fruits and seeds (Hegedús et al., 2013).

Phoenix dactylifera

Phoenix dactylifera L. (Family of Arecaceae) is one of the oldest plants cultivated in the Arabian region and in other parts of the world. In Morocco, 4.8 million trees of date palm groves occupy a surface area of more than 48,000 ha (Sedra et al., 2011). Due to their health promoting properties, the fruits of date palm were used as food and as remedy in folk medicine. The phytochemical screening of leaf, fruit, seeds and bark of date palm contains high quantity of secondary metabolites like flavonoids, steroids, saponins and tannins (Al-daihan et al., 2012). Date fruit is characterized by a high energy content, carbohydrates (Myhara et al., 2000), lipids, proteins, and are an excellent source of dietary fiber and certain essential vitamins and minerals (Khalid et al., 2017).

This richness leads to many *in-vitro* and *in-vivo* pharmacological studies as well as the identification and quantification of different classes of bioactive compounds (Chao et al., 2007). In our investigation we found that *P. dactylifera* has been reported to contain five potent anti-coronavirus molecules which are procyanidin B1, kaempferol, β -sitosterol, quercetin, and luteolin (Table 3). In the study conducted by Hong et al. (HongYun et al., 2006), the authors reported the presence of thirteen glycosylated flavonoids of luteolin, quercetin along with procyanidins at different stages of maturity.

The bioactive compounds of *P. dactylifera* have gained increased interest among several investigators due to their antioxidant (Biglari et al., 2004), antimutagenic (Vayalil et al., 2002), anti-diabetic (Mard et al., 2010), and anti-inflammatory (Zhang et al., 2013), anti-tumor (Ishurd et al., 2005), as well as cholesterol-lowering properties and other potential health benefits such as prevention of cardiovascular diseases and chemoprevention of cancer (Chao et al., 2007). Moreover, the study conducted by Jassim and Naji, (Jassim et al., 2010) revealed antiviral activity of date pits extract against lytic Pseudomonas phage ATCC 14209-B1, with minimum inhibitory concentration of 10 μ g/ml. In light of the above, antiviral studies of *Phoenix dactylifera* phytochemicals should be extended to other viruses that threaten human health.

Punica granatum

Punica granatum (Pomegranate) is a small tree belonging to the family of *Punicaceae*. This plant is largely distributed in parts of Asia, North Africa and in the Middle East (Hmid et al, 2017). In Morocco, the pomegranate is cultivated on an area of 5000 ha, which give rise to a yield of 58,000 tons of fruits per

year (Oukabli et al., 2004). The fruit of *P. granatum* can be consumed fresh or after transformation to juices or beverages. *P. granatum* has been widely used as a traditional medicine for the treatment of microbial infections, respiratory pathologies, dysentery, hemorrhage, and diarrhea (EM et al., 2009). Moreover, the dried pericarp of *P. granatum* was also reported to cure colitis, headache, acne, and oral diseases (Ricci et al., 2006).

The different parts of the *P. granatum* contain various phytochemicals with various pharmacological activities. In fact, the chemicals reported in this medicinal plant possess antioxidant properties, anti-inflammatory and anti-mutagenic effects, and antiviral, antibacterial, anti-angiogenesis, and anticancer activities (Rahimi et al., 2012; Mestry et al., 2017).

The juice of *P. granatum* is rich in flavonoids including phenolic acids and anthocyanins, and the pericarps contain ellagitannins and tannins (Kim et al., 2002). It should be noted that the juice of *P. granatum* is obtained by pressing the whole fruits, which results in an enrichment of this juice by polyphenols from the pericarp.

Interestingly, *P. granatum* contains six molecules that were reported to have potent anti-coronavirus activities and which are, procyanidin B1, β -sitosterol, betulinic acid, quercetin, luteolin, and Kaempferol (Table 3).

Mentha longifolia

HPLC analysis of *Mentha longifolia* L. highlights their importance as a promising source of five anticoronavirus ingredients: β -sitosterol, kaempferol, quercetin, luteolin, and hesperetin (Table 3). The genus *Mentha longifolia* L. (syn. *M. spicata* var. *longifolia* L., *M. sylvestris* L., *M. tomentosa* D'Urv, *M. incana* Willd.) belonging to the *Lamiaceae* family, is a perennial spice plant being indigenous to temperate and Mediterranean regions of Eurasia and northern and southern Africa (Elansary et al., 2020). The *Mentha* genus plants are very popular for humankind since antiquity and is one of the most widely used herbal medicines. Many parts of this genus, including leaves, flowers and stems, are used in herbal teas and condiments due to their distinct flavor and aroma (Gulluce et al., 2007). In Morocco, *Mentha* species are widely used as food, medicine, spice, and flavoring agents. Contrary to its abundance, *Mentha longifolia* is less known and rarely used in Europe and was not industrialized (Patonay et al., 2019).

In herbal remedies, *M. longifolia* L. was reported as an important crop widely consumed due to its health-promoting properties, for the treatment of many infectious and inflammatory diseases as well as for respiratory and gastrointestinal disorders (Farzaei et al., 2017). Therefore, many bioactive molecules present in *M. longifolia* are in part responsible for these consequent therapeutic benefits. As well, the phytochemical characterization of this medicinal plant revealed a vast variety of natural components that have been suggested to be responsible for the pharmacological potent of *M. longifolia*. These molecules include flavonoids, terpenoids, phenolic acids, sesquiterpenes cinnamates, and ceramides, (Farzaei et al., 2017). As a result, various pharmacological investigations for *M. longifolia* extracts have been confirmed their potential effects, as antioxidant (Bahadori et al., 2018), anti-inflammatory (Karimian et al., 2013),

anti-parasitic (Farzaei et al., 2017), cytotoxic and antimicrobial (Elansary et al., 2020) agents. Moreover, it has been shown that flavonoids from *M. longifolia* such as luteolin-7-O-glycoside, luteolin-7,3'-O-diglycoside, quercetin-3-O-glycoside and kaempferol-3-O-glycoside are potent inhibitors of some microorganisms that may be causal agents of human urinary, intestinal and respiratory tract infections (Bendjeddou et al., 2009). This herb exhibited therapeutic benefits as antiviral (El-badry et al., 2010) as well, with high HIV 1 inhibitory properties.

Salvia officinalis

Sage (*Salvia officinalis* L.) which is named in Morocco "Salmia", is a potent aromatic and medicinal plant used in folk medicine, phytopharmaceutical preparations and aromatherapy (Hamidpour et al., 2014). The sage is rich in various secondary metabolites such as phenolic and volatile compounds. Furthermore, *S. officinalis* L. possesses different biological properties such as antioxidant (Ghorbani et al., 2017), anti-inflammatory activities (Rodrigues et al., 2012), and reported to have antitumor (Garcia et al., 2016), antibacterial (Stagos et al., 2012), and antifungal effects (Badiie et al., 2012). As well, the aerial parts of *S. officinalis* have been also provided to act as potent antiviral against vesicular stomatitis virus (Tada et al., 1994). Moreover, methanolic extract of sage showed antiviral activity against herpes simplex, Sindbis and polio viruses, with minimum inhibitory concentration of 50 µg/ml (Mouhajir et al., 2001).

Remarkably, *S. officinalis* contains six molecules that were reported to have potent anti-coronavirus activities and which are, gallic acid, gallic acid gallate, betulinic acid, kaempferol, quercetin, luteolin, hesperetin (Table 3).

Rosmarinus officinalis

Rosmarinus officinalis L. (*Lamiaceae* family), also known as rosemary, is an edible, evergreen, medicinal plant. Native species of this herb spread spontaneously in the Mediterranean area (Carrubba et al., 2020)]. This plant is exploited in traditional medicine for its antioxidant activity ascribable to bioactive compounds (Andrade et al., 2018). In fact, there are many studies on the usefulness of bioactive substances of rosemary plants on human health as it was used to treat arthritis, diabetes, memory loss and hair restoration (El Omri et al., 2010). Rosemary has a great potential due to secondary biomolecules which have been characterized as antidiabetic (Yen et al., 2015), antimicrobial (Almela et al., 2006), spasmolytic, carminative, hepatoprotective, antiviral and anticarcinogenic agents (Bozin et al., 2007), and reported also to have antihyperglycemic, anti-inflammatory and antiproliferative activities (Oliveira et al., 2019). Some rosemary extracts have been shown strong inhibitory effect against human respiratory syncytial virus infection (Shin et al., 2013). Furthermore, an *in vitro* antiviral effect, against herpes simplex virus types 1 and 2, have been proved by aqueous extract of this species (Nolkemper et al., 2006).

In our investigation, we found that *Rosmarinus officinalis* could be a potent anti-SARS-CoV-2 as it contains molecules such as kaempferol, hesperetin, quercetin, luteolin and betulinic acid (Table 3).

Portulaca oleracea

Portulaca oleracea L. belongs to the family of *Portulacaceae*. This plant which is largely distributed in tropical and temperate regions worldwide, has been widely used in traditional medicine to treat different diseases including severe inflammations, respiratory problems, and headaches (Zhu et al., 2010; Iranshahy et al., 2017). Bioactive molecules could be of different nature as this plant is rich in flavonoids, terpenoids, alkaloids, organic acids, and vitamins (Zhou et al., 2015). This annual succulent plant is used in several countries as soups and salads (Iranshahy et al., 2017 ; Miao et al., 2019).

While the aerial parts were used to cure inflammations of the urinary system, intestinal ulcers, high cholesterol level, cough and was also used for its anti-oxidant and anti-microbial properties (Dan et al., 2006). Oral administration of *P. oleracea* seeds was used for the treatment of respiratory problems, spermatorrhea and fevers in Spain as it was stated by Abulcasis (Al-Zahrawi, Arab-Andalusian physician (936–1013)) (Iranshahy et al., 2017). In a recent study conducted by Li et al. (Li et al., 2019), the authors reported an anti-IAV (influenza A virus) of the water extract of *P. oleracea* and recommended the use of this extract as an herbal diet for the prevention and treatment of H1N1 infection at an early stage.

In Africa, *P. oleracea* is used to cure different diseases including gastric problems, diabetes, hypertension, spastic paralysis, etc (Iranshahy et al., 2017). It is also used for the preparation of salad in Morocco by mixing its shoots with garlic, green olives, olive oil and some spices (Benkhniqie et al., 2010). In Morocco, *P. oleracea* is also used as an energizing food (Bachar et al., 2016).

Studies of acute toxicity on mice have showed that *P. oleracea* is moderately toxic with LD₅₀ value of 1853 mg/kg (Iranshahy et al., 2017). Moreover, no adverse effects have been detected on most clinical trials.

In our investigation from literature, we found that *P. oleracea* contains five potent anti-coronavirus molecules, which are β -sitosterol, quercetin, hesperetin, luteolin, and kaempferol (Table 3).

Conclusion

Alternative Medicine has accumulated thousand-of-year's experiences to treat pandemic viral infections. The SARS-CoV-2 is spreading at a rate and scale much worse than previous emerging coronavirus SARS or MERS, and continue to become a global burden on human health. So, there is an urgent need to find some efficacious treatments against SARS-CoV-2 infection. Providing complementary or alternative treatments are still urgently needed to manage COVID-19 disease.

In brief, this study offers a powerful, integrative network-based pharmacology methodology for rapid identification of potent natural compounds against the SARS-CoV-2. As well, among 41 natural molecules screened, the molecular docking results showed 13 molecules to be orally bioactive and exhibiting potential abilities as inhibitors of the proteases PLpro, 3CLpro, and protein S targets of the novel coronavirus. Moreover, most of these molecules showed high binding abilities to more than one protein and suggest a more pronounced effect for those molecules against the SARS-CoV-2. Moreover, 29 Moroccan medicinal plants were found to contain 3 to 6 of these molecules including, kaempferol,

quercetin, hesperetin, luteolin, procyanidin B1, aloe emodin, betulinic acid and β -sitosterol. From the 29 plants, 8 of them have been chosen as they might contain direct anti-SARS-CoV-2 molecules including: *Argania spinosa* L., *Cydonia oblonga*, *Phoenix dactylifera*, *Punica granatum*, *Portulaca Oleracea*, *Mentha longifolia*, *Salvia officinalis*, and *Rosmarinus officinalis* L.

Based on these results, our study reports for the first time a selection of Moroccan Medicinal plants that could contain direct anti-SARS-CoV-2 compounds by targeting the 3CLPro, PLpro proteases and the protein S of this virus.

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Tables

Table 1. The natural compounds and their binding energy (kcal/mol) against proteins of the SARS-CoV-2

Family/Molecular name	Targets or inhibition	Origine	Reference	Docking (binding energy) Affinity (kcal/mol)		
				PL ^{pro}	3CL ^{pro}	Protein S
Flavonoids						
Baicalin	SARS-CoV	<i>Scutellaria baicalensis</i>	(Chen et al., 2004)	-7.7	-8.1	-8.5
Hesperetin	3CL ^{pro}	Pure compound	(Lin et al., 2005)	-6.8	-7.3	-7.9
Kaempferol	3CL ^{pro} & PL ^{pro}	Pure compound	(Park et al., 2017)	-6.7	-7.7	-7.5
Luteolin	3CL ^{pro}	Pure compound	(Ryu et al., 2020)	-6.9	-7.5	-8.7
Quercetin	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-7.1	-9	-8.6
Procyanidin b1	protein S	<i>Cinnamomi Cortex</i>	(Zhuang et al., 2009)	-8	-9.3	-10.4
4-hydroxyderricin	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-6.8	-6.4	-6.4
4'-O-methylbavachalcone	PL ^{pro}	<i>Psoralea corylifolia</i>	(Kim et al., 2014)	-6.8	-7.1	-6
Amentoflavone	3CL ^{pro}	<i>T. nucifera leaves</i>	(Ryu et al., 2020)	-8.9	-9.8	-10.2
Ampelopsin	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-6.7	-7.3	-7.8
Bavachinin	PL ^{pro}	<i>Psoralea corylifolia</i>	(Kim et al., 2014)	-7.3	-7.7	-8.2
Corylifol A	PL ^{pro}	<i>Psoralea corylifolia</i>	(Kim et al., 2014)	-8.1	-7.1	-7.3
Daidzein	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-7.1	-7.2	-7.1
Epigallocatechin	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-6.8	-7.2	-7.9
Gallocatechin gallate	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-7.6	-9.1	-8.8
Isobavachalcone	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-7.4	-7.2	-7
Neobavaisoflavone	PL ^{pro}	<i>Psoralea corylifolia</i>	(Kim et al., 2014)	-8	-7.4	-7.9
Neodiosmin	3CL ^{pro}	<i>Limes</i>	(Sun et al., 2020)	-7.6	-8.5	-9.5
Procyanidin A2	Protein S	<i>Cinnamomi Cortex</i>	(Zhuang et al., 2009)	-7.7	-9.4	-9.2
Puerarin	3CL ^{pro}	Pure compound	(Nguyen et al., 2012)	-6.8	-7.4	-7.3
Rutin	3CL ^{pro}	<i>Widely found in plants</i>	(Sun et al., 2020)	-7.6	-8.8	-9.7
Sinigrin	3CL ^{pro}	<i>Isatis indigotica root</i>	[15]	-5.6	-6.4	-6.2
Xanthoangelol G	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-4.7	-6.4	-6.8

Xanthokeistal A	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-5.9	-5.8	-5.3
Chalconoids						
Xanthoangelol	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-7.4	-7.3	-7.8
Xanthoangelol B	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-6.3	-6.9	-6.6
Xanthoangelol D	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-6.7	-6.1	-6.2
Xanthoangelol E	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-6.7	-6.4	-7.1
Xanthoangelol F	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-6.9	-6.5	-6.5
Furocoumarins						
Bergapten	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-5.7	-5.8	-6.3
Psoralen	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-5.7	-5.9	-6.3
Xanthotoxin	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-5.7	-6.1	-6.4
Isopimpinellin	3CL ^{pro} & PL ^{pro}	<i>Angelica keiskei</i>	(Park et al., 2016)	-5.8	-5.8	-6.3
Triterpene						
Betulinic acid	3CL ^{pro}	Pure compound	(Wen et al., 2007)	-7.7	-7.5	-7.5
Alkaloid						
Lycorine	Sars-Cov	<i>Lycoris radiata</i>	(Li et al., 2005)	-6.8	-7.5	-7.9
Polyphenolic acids/Coumpounds						
Psoralidin	PL ^{pro}	<i>Psoralea corylifolia</i>	(Kim et al., 2004)	-7.9	-7.5	-8.4
Chlorogenic acid	SARS-CoV	<i>Flos Lonicerae</i>	(Chen et al., 2004)	-7.6	-7	-8.6
Sterol						
β-sitosterol	3CL ^{pro}	<i>Isatis indigotica root</i>	Lin et al., 2005	-6.7	-6.5	-6.4
Hydroxyanthraquinone Aloe-emodin	3CL ^{pro}	Pure compound	(Lin et al., 2005)	-6.5	-7	-8.1
Others						
Neonuezhenide	3CL ^{pro}	<i>Fruits of Ligustrum lucidum</i>	(Sun et al., 2020)	-7.7	-7.7	-7.5
Specnuezhenide	3CL ^{pro}	<i>Fruits of Ligustrum lucidum</i>	(Sun et al., 2020)	-7.5	-8.5	-8.6

PL^{pro}: papain-like protease; 3CL^{pro}: 3C-like protease; protein S: Spike protein

The 13 compounds that have been successfully passed the ADME screening are in bold

Table 2. Pharmacokinetic Parameters of the selected natural compounds

Molecule	Oral bioavailability (%)	Caco-2 permeability	Drug-likeness 0.18
Aloe-emodin	83.38	-0.12	0.24
Baicalin	40.12	-0.85	0.75
Bergapten	42.21	1.05	0.1
β -sitosterol	36.91	1.32	0.75
Betulinic acid	55.38	0.73	0.78
Hesperetin	70.31	0.37	0.27
Kaempferol	41.88	0.26	0.24
Luteolin	36.16	0.19	0.25
Psoralen	33.06	1.05	0.1
Psoralidin ¹	-	-	-
Quercetin	46.43	0.05	0.28
Xanthotoxin	35.3	1.05	0.13
Procyanidin B1	67.87	-0.98	0.66

¹ This molecule was tested for its oral bioavailability by Sun et al. (Sun et al., 2015)

Table 3. Moroccan Medicinal plants contains anti-sars-cov-2 molecules targeting PL^{pro}, 3CL^{pro} and protein S

Family	Plant name	Molecule	Targets		
			PL ^{pro}	3CL ^{pro}	Protein S
<i>Clusiaceae</i>					
	<i>Opuntia Ficus-Indica</i>	β -sitosterol		v	
		Kaempferol	v	v	
		Quercetin		v	
		Luteolin		v	
<i>Sapotaceae</i>					
	<i>Argania spinosa</i>	Procyanidin B1			v
		Kaempferol	v	v	
		Betulinic acid		v	
		Quercetin		v	
		Luteolin		v	
<i>Rosaceae</i>					
	<i>Cydonia oblonga</i>	Procyanidin B1			v
		β -sitosterol		v	
		Kaempferol	v	v	
		Betulinic acid		v	
		Luteolin		v	
<i>Areaceae</i>					
	<i>Phoenix dactylifera</i>	Procyanidin B1			v
		β -sitosterol		v	
		Kaempferol	v	v	
		Quercetin		v	
		Luteolin		v	
<i>Myrtaceae</i>					
	<i>Myrtus communis</i>	Procyanidin B1			v
		β -sitosterol		v	
		Kaempferol	v	v	
<i>Punicaceae</i>					
	<i>Punica granatum</i>	Procyanidin B1			v
		β -sitosterol		v	
		Kaempferol	v	v	
		Betulinic acid		v	

	Quercetin		v
	Luteolin		v
<hr/>			
<i>Lamiaceae</i>			
<i>Thymus vulgaris</i>	Aloe emodin		v
	Luteolin		v
	Quercetin		v
<hr/>			
<i>Mentha longifolia</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
	Hesperetin		v
<hr/>			
<i>Salvia officinalis</i>	Gallocatechin gallate		v
	Kaempferol		
	Quercetin	v	v
	Luteolin		v
	Betulinic acid		v
	Hesperetin		v
<hr/>			
<i>Rosmarinus officinalis L</i>	Quercetin		v
	Luteolin		v
	Betulinic acid		v
	Hesperetin		v
	Kaempferol	v	v
<hr/>			
<i>Mentha pulegium</i>	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
<hr/>			
<i>Portulacaceae</i>			
<i>Portulaca Oleracea</i>	β -sitosterol		v
	Quercetin		v
	Hesperetin		v
	Luteolin		v
	Kaempferol	v	v
<hr/>			
<i>Asteraceae</i>			
<i>Achillea ligustica</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v

	Luteolin		v
<i>Dittrichia viscosa</i>	Luteolin		v
	Quercetin		v
	Hesperetin		v
	Kaempferol	v	v
Apiaceae			
<i>Ammi majus</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
<i>Coriandrum sativum</i>	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
Euphorbiaceae			
<i>Euphorbia guyoniana</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v
Pedaliaceae			
<i>Sesamum indicum L</i>	β -sitosterol		v
	Kaempferol	v	v
	Luteolin		v
	Hesperetin		v
Ranunculaceae			
<i>Nigella Sativa</i>	β -sitosterol		v
	Kaempferol	v	v
	Luteolin		v
	Quercetin		v
Verbenaceae			
<i>Vitex agnus-castus</i>	β -sitosterol		v
	Kaempferol	v	v
	Luteolin		v
Fabaceae			
<i>Ceratonia siliqua</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v

	Luteolin		v
<i>Retama monosperma</i>	β -sitosterol		v
	Luteolin		v
	Kaempferol	v	v
	Quercetin		v
<i>Retama raetam</i>	Kaempferol	v	v
	Luteolin		v
	Quercetin		v
<i>Aloe vera</i>	Kaempferol	v	v
	Luteolin		v
	Quercetin		v
<i>Lythraceae</i>			
<i>Lawsonia inermis</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
<i>Cupressaceae</i>			
<i>Juniperus oxycedrus</i>	β -sitosterol		v
	Kaempferol	v	v
	Quercetin		v
<i>Brassicaceae</i>			
<i>Anastatica hierochuntica</i>	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
<i>Iridaceae</i>			
<i>Crocus sativus</i>	Kaempferol	v	v
	Quercetin		v
	Luteolin		v
<i>Rhamnaceae</i>			
<i>Rhamnus alaternus</i>	Kaempferol	v	v
	Luteolin		v
	Quercetin		v

The eight selected plants were marked in bold.

Figures

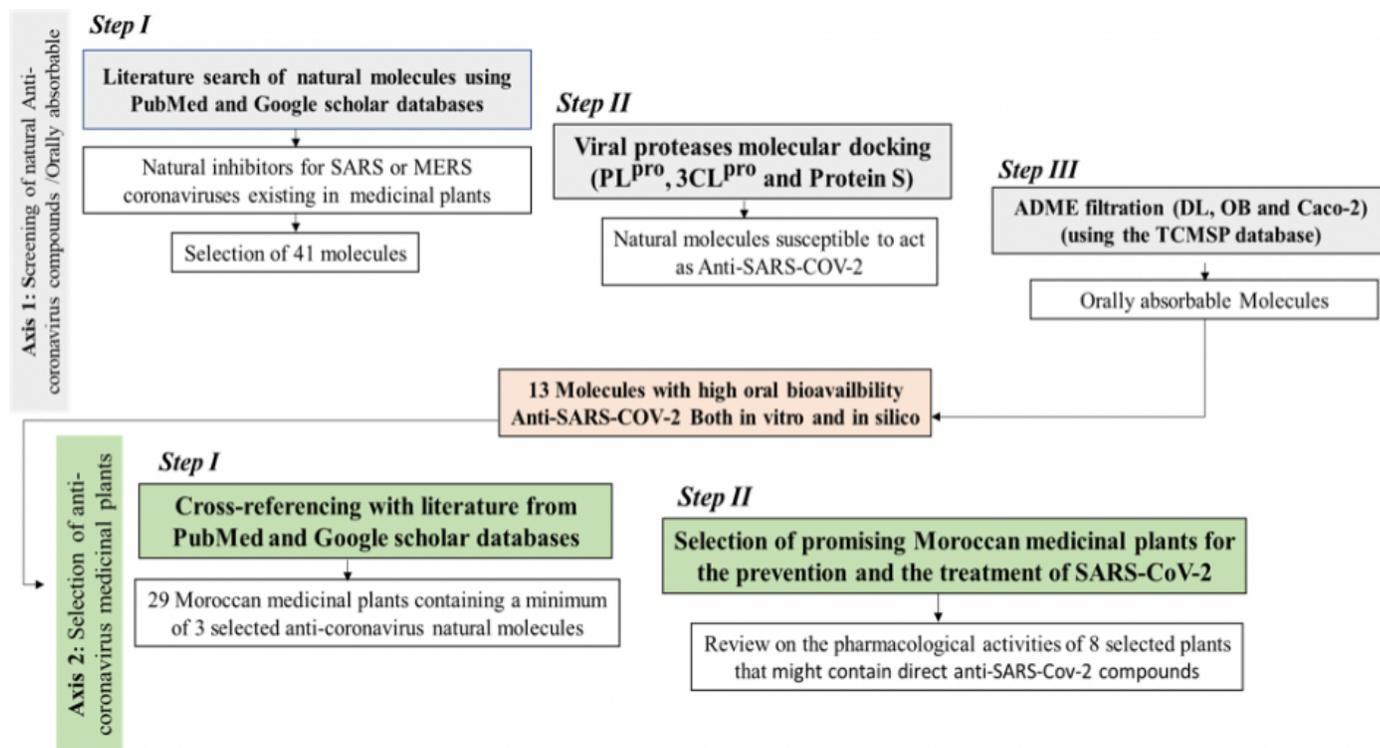


Figure 1

Scheme 1. Workflow scheme illustrating the multistep screening process for the selection of Moroccan medicinal plants supposed to contain potent natural inhibitors to the SARS-CoV-2