



## Natural products from the traditional Moroccan pharmacopoeia: A potential lead for the prevention and treatment of COVID-19

Mohamed Yafout\*, Amine Ousaid, Ibrahim Sbai El Otmani, Youssef Khayati, Amal Ait Haj Said

Laboratory of Drug Sciences, Biomedical and Biotechnological Research, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Casablanca, Morocco



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### ABSTRACT

The new SARS-CoV-2 belonging to the coronaviruses family has caused a pandemic affecting millions of people around the world. This pandemic has been declared by the World Health Organization as an international public health emergency. Although several clinical trials involving a large number of drugs are currently underway, no treatment protocol for COVID-19 has been officially approved so far. Here we demonstrate through a search in the scientific literature that the traditional Moroccan pharmacopoeia, which includes more than 500 medicinal plants, is a fascinating and promising source for the research of natural molecules active against SARS-CoV-2. Multiple *in-silico* and *in-vitro* studies showed that some of the medicinal plants used by Moroccans for centuries possess inhibitory activity against SARS-CoV or SARS-CoV-2. These inhibitory activities are achieved through the different molecular mechanisms of virus penetration and replication, or indirectly through stimulation of immunity. Thus, the potential of plants, plant extracts and molecules derived from plants that are traditionally used in Morocco and have activity against SARS-CoV-2, could be explored in the search for a preventive or curative treatment against COVID-19. Furthermore, safe plants or plant extracts that are proven to stimulate immunity could be officially recommended by governments as nutritional supplements.

### \*Corresponding Author

Name: Mohamed Yafout

Phone: +212661472976

Email: yafoutm@yahoo.fr

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### INTRODUCTION

Coronaviruses are positive-sense, single-stranded RNA enveloped viruses belonging to the Nidovirales order and the Coronaviridae family. They can cause respiratory, digestive and nervous dis-

eases in humans and animals (Weiss and Navas-Martin, 2005). The coronavirus affecting humans can cause both benign manifestations and serious diseases such as the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (Ksiazek et al., 2003; Fehr and Perlman, 2015).

In December 2019, a new coronavirus named SARS-CoV-2 or 2019-nCoV caused an outbreak associated with pneumonia in Wuhan, China (Lu et al., 2020). The drastic containment measures have not prevented the disease from turning into a pandemic affecting many countries around the world. On Oct 4, 2020, the total cumulative number of cases worldwide has exceeded 34 million, and the number of deaths from SARS-CoV-2 exceeded a million (W.H.O., 2020).

At present, although several drugs have already

been incorporated into the management protocols of COVID-19 in some countries, no specific treatment is formally approved by the World Health Organization (WHO, 2020).

Several clinical trials are underway across the world and concern a multitude of already known drugs (Lopinavir / Ritonavir, Oseltamivir, Favipiravir, Remdesivir, Chloroquine, Hydroxychloroquine, Azithromycin, Tocilizumab, Interferon- $\beta$ , etc.) (U.S. National Library of Medicine, 2020). To date, none of these drugs has demonstrated clinically proven efficacy against SARS-CoV-2.

Natural products, mainly of plant origin, have always been an inexhaustible source of molecules which have given rise to countless medicines. Thus, medicinal plants and derived products which have activity against coronaviruses could offer interesting leads for the discovery of an effective treatment against COVID-19. In this sense, the traditional Moroccan pharmacopoeia contains more than five hundred plant species used for centuries (Bellakhdar, 1997).

In this review of the literature, plants, plant extracts or natural molecules with potential activity against SARS-CoV or SARS-CoV-2 are discussed to emphasise the interest of exploring their utility in the prevention or treatment of COVID-19.

## METHOD

First, we identified the best-known and more used medicinal plants (Table 1) in Morocco from a reference book (Bellakhdar, 1997). Then, we searched the PubMed database using the keywords "scientific plant name + SARS-CoV". Given the similarity of the molecular mechanisms of SARS-CoV-2 and SARS-CoV (Rabaan et al., 2020), the results for the latter will also be considered in this review.

## RESULTS

The research that was carried out yielded the following results:

### Direct action on the virus

#### Plants and plant extracts

A study on the aqueous extract of green tea (*Camellia sinensis*), demonstrated an inhibitory activity on the 3CLpro protease of SARS-CoV-2 with an IC50 (Inhibitory concentration 50) of  $8.9 \pm 0.5$   $\mu\text{g/ml}$ . This activity could significantly slow down the virus's replication cycle. The in-silico analysis suggests that the arubigins could be the active molecules in the extract (Upadhyay et al., 2020).

Laurel (*Laurus nobilis*), Juniper (*Juniperus oxycedrus*) and sage (*Salvia officinalis*) are plant species

very well-known and widely used in Morocco as traditional remedies (Bellakhdar, 1997). A study was able to demonstrate variable antiviral activities against SARS-CoV of essential oils extracted from these plants with respective IC50s of 120  $\mu\text{g/ml}$ , 270  $\mu\text{g/ml}$  and 870  $\mu\text{g/ml}$ . Analysis of the composition of the essential oil of laurel, which demonstrated the highest antiviral activity, reveals  $\beta$ -ocimene and 1,8-cineole as main compounds (21.83% and 9.43% respectively). The parts have been used for the extraction of oils are berries (Laurel and juniper) and the leaves (Sage) (Loizzo et al., 2008).

Geraniums (*Pelargonium odoratissimum*, *Pelargonium roseum*, *Pelargonium capitatum* and *Pelargonium graveolens*) and lemon (*Citrus limon*) are plants that have been used for a very long time in Morocco. The distilled water and the essential oil derived from these plants are traditionally used for cosmetic, aromatic and medical aims (Bellakhdar, 1997; Chraïbi et al., 2018). In an in-vitro study, the essential oils of *Pelargonium graveolens* and *Citrus limon* showed inhibitory activity. They reduced the concentration and expression of Angiotensin-Converting Enzyme 2 (ACE2) in HT-29 cells at respective concentrations of 50  $\mu\text{g/ml}$  and 25  $\mu\text{g/ml}$ . ACE2 is an enzyme that plays a crucial role in the entry of SARS-CoV-2 into host cells. On the other hand, the major constituents of the two essential oils (Citronellol, limonene, geraniol and neryl acetate) have shown the same properties as the essential oils towards ACE2. It should be noted that neither the two essential oils nor their major components studied showed cytotoxicity towards the HT-29 cells (Kumar et al., 2020).

Beans (*Vicia faba*) and sesame seeds (*Sesamum indicum*) are foods highly appreciated by Moroccans for their high nutritional value. They are known for their high content of unsaturated fatty acids, including linoleic acid (Bellakhdar, 1997; Khalil et al., 2020). Furthermore, it was demonstrated that unsaturated fatty acids could inactivate enveloped viruses by action on the double lipid envelope (Kohn et al., 1980).

#### Molecules derived from plants

##### Heterosides

The oleander (*Nerium Oleander*) is a plant known in Morocco for its traditional use in specific diseases but also for its toxicity (Tahraoui et al., 2007). It contains a heteroside called "Oleandrin". In an in vitro study on Vero cells (Plante et al., 2020), the administration of oleandrin at doses of 50ng/ml and 100ng/ml resulted in significant inhibition of viral replication both before and after viral infection with

**Table 1: Classification by botanical family of plants cited in the review**

Botanical family	Plant scientific name	Plant common name
Apocynaceae	<i>Nerium oleander</i>	Oleander
Asteraceae	<i>Artemisia herba alba</i>	White mugwort
Camelliaceae	<i>Camellia sinensis</i>	Green tea
Cupressaceae	<i>Juniperus oxycedrus</i>	Juniper
Fabaceae	<i>Glycyrrhiza glabra</i>	Licorice
	<i>Vicia faba</i>	Beans
	<i>Acacia senegal</i>	Gum acacia
Geraniaceae	<i>Pelargonium odoratissimum</i>	Geranium
	<i>Pelargonium roseum</i>	<i>Pelargonium capitatum</i>
	<i>Pelargonium graveolens</i>	
Lamiaceae	<i>Salvia officinalis</i>	Sage
Lauraceae	<i>Laurus nobilis</i>	Laurel
Liliaceae	<i>Allium sativum</i>	Garlic
Pedaliaceae	<i>Sesamum indicum</i>	Sesame
Piperaceae	<i>Piper nigrum</i>	Black pepper
Renonculaceae	<i>Nigella sativa</i>	Black cumin / Black seed
Rutaceae	<i>Citrus aurantium var. amara</i>	Bitter orange
	<i>Citrus aurantium var. bergamia</i>	Bergamot
	<i>Citrus limon</i>	Lemon
	<i>Citrus limetta</i>	Lime
Urticaceae	<i>Urtica dioica</i>	Stinging nettle
Zingiberaceae	<i>Curcuma longa</i>	Turmeric
	<i>Zingiber officinale</i>	Ginger

SARS-CoV-2.

### Terpenes

The white mugwort (*Artemisia herba alba*) is a plant widely used in traditional Moroccan medicine (Amor *et al.*, 2019). A molecular docking study has shown that artemisinin, a sesquiterpene lactone derived from white mugwort has a higher score than hydroxychloroquine in binding sites with the Spike protein which is the key which allows SARS-CoV-2 to enter cells. The analysis of the molecular dynamics showed that the bonds formed are stable (Sehailia and Chemat, 2020).

The Thymoquinone and dithymoquinone are the main active ingredients contained in the seeds of *Nigella sativa*, a herbal drug also widely used by Moroccans for the treatment of various diseases (Bellakhdar, 1997; Ghosheh *et al.*, 1999). The results of an in-silico molecular simulation study showed that Thymoquinone could have inhibitory activity towards the protease of SARS-CoV-2 (Kadil *et al.*, 2020). In another study, dithymoquinone (DTQ) showed by molecular docking analysis an affinity for ACE2 of SARS-CoV-2 greater than that of Chloroquine and other main components of *Nigella sativa*. Molecular dynamics subsequently confirmed

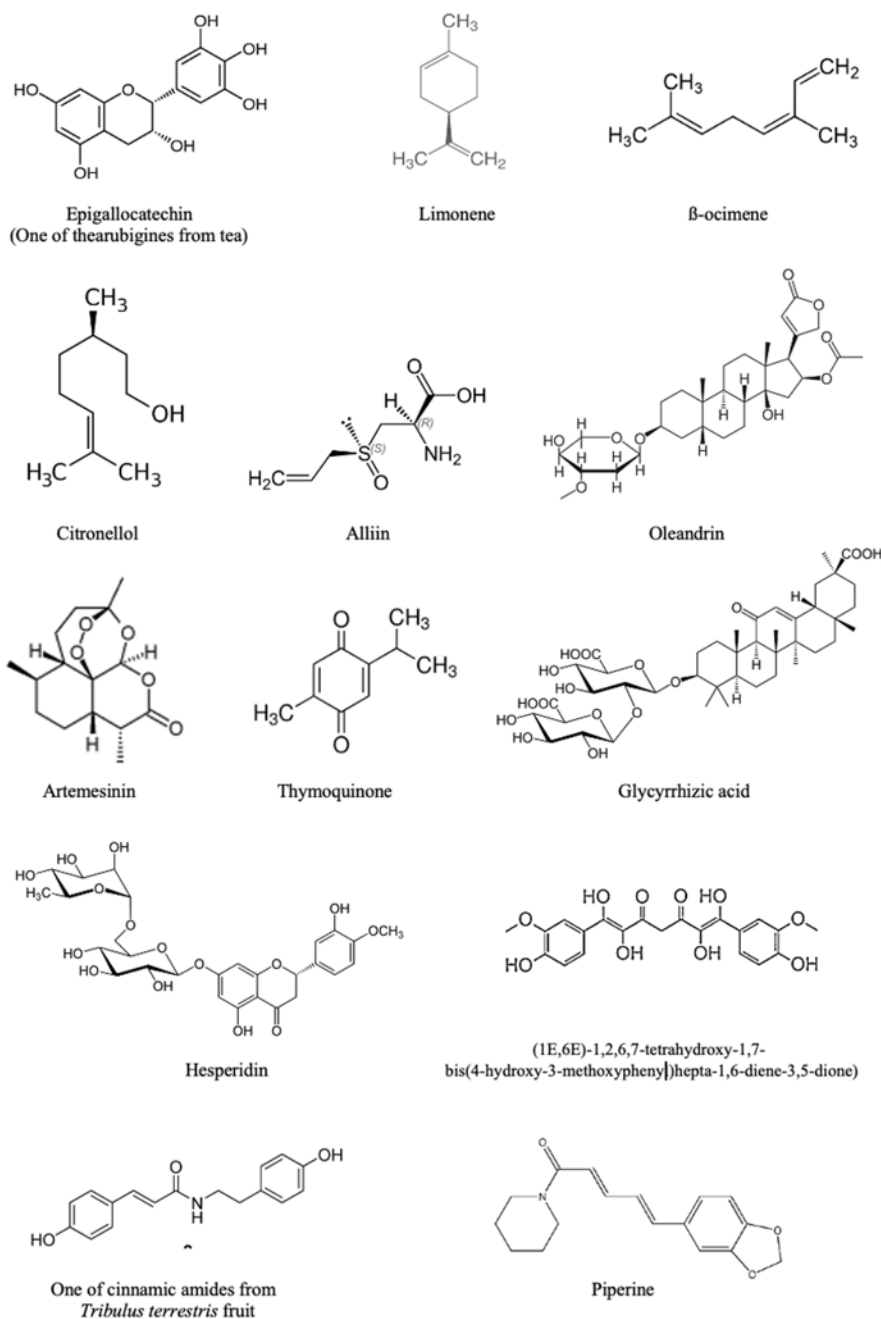
the stability of the DTQ-ACE2 binding. These results are in favour of possible inhibitory activity of DTQ towards the ACE2 (Ahmad *et al.*, 2020).

### Saponosides

Glycyrrhizin is a molecule derived from Licorice (*Glycyrrhiza glabra*) whose root is used by Moroccans for its medicinal properties (Bellakhdar, 1997). A study carried out in Germany in 2003 evaluated in vitro on Vero cells, the antiviral potential of several molecules. Glycyrrhizin was found more active than ribavirin, 6-aziridine, pyrazofurin and the Mycophenolic acid (Cinatl *et al.*, 2003). Another study aimed at identifying in-silico the activity of molecules derived from licorice against two targets of SARS-CoV-2, the Spike protein and the endoribonuclease Nsp 15, has shown, via the analysis of molecular docking and molecular dynamics, that Glycyrrhizic Acid has a high affinity which can inhibit the Spike protein of SARS-CoV-2 (Sinha *et al.*, 2020).

### Polysaccharides

*Acacia senegal* is a tree from which gum arabic is extracted. Gum Arabic is used for medicinal purposes in Saharan regions (Bellakhdar, 1997; Azzaoui *et al.*, 2015). It contains a polysaccharide called



**Figure 1: Chemical structures of some natural molecules cited in the review**

arabic acid. In an in-silico study, it was demonstrated by molecular docking that arabic acid is a potent inhibitor of the 3CLpro protease of SARS-CoV-2. Molecular dynamics simulations have shown that the binding of arabic acid in the 3CLpro causes structural perturbations that promote the inhibitory potential (Dwarka et al., 2020).

### Flavonoids

Hesperidin is a flavonoid present in abundance in

the fruit of plants belonging to the genus *Citrus*, traditionally used in Morocco. These include bitter orange and bergamot (*Citrus aurantium*), lemon (*Citrus limon*) and sweet lime (*Citrus limetta*) (Bel-lakhdar, 1997).

Hesperidin is of great interest because it can bind to the main proteins of SARS-CoV-2. This has been proven by several studies based on molecular simulations that have shown that hesperidin has a higher binding affinity than lopinavir, ritonavir and indi-



navir with both the spike protein and the protease 3CLpro (Bellavite and Donzelli, 2020).

### Lectins

The stinging nettle (*Urtica dioica*) is a medicinal plant widely used in Morocco (Bellakhdar, 1997; Bnouham et al., 2003). The lectin obtained from this plant demonstrated in an in-vitro study an antiviral effect against SARS-CoV in Vero cells with an EC<sub>50</sub> of 1.3 µg/ml and a selectivity index of 77 demonstrating the absence of toxicity. The most likely mechanism of action would be an interference between the lectin of *Urtica dioica* and the glycans of SARS-CoV Spike protein of (Keyaerts et al., 2007).

### Curcuminoids

Curcuminoids are compounds contained in turmeric (*Curcuma longa*), a plant whose rhizome is used in Morocco for its medicinal properties and culinary purposes (Bellakhdar, 1997; Skalli et al., 2019). A study based on molecular docking and molecular dynamics simulations showed that two curcuminoid compounds present in turmeric ((1E, 6E)-1,2,6,7-tetrahydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) and (4Z, 6E)-1,5-dihydroxy-1,7-bis(4-hydroxyphenyl) hepta-4,6-dien-3-one) whose structure is close to curcumin, have a good bond with the catalytic domain of SARS-CoV-2 Mpro protein (Gupta et al., 2020).

### Cinnamic amides

Although toxic and rarely used in traditional medicine, *Tribulus Terrestris* is a plant known in Morocco (Bellakhdar, 1997). In an in-vitro study, the methanolic extract of the fruit of *Tribulus Terrestris* showed a capacity for inhibiting the PLpro protease of SARS-CoV. Separation by chromatography of the components of this methanolic extract revealed six cinnamic amides all possessing an inhibitory activity towards the PLpro protease of SARS-CoV. Among the six compounds, the one with the highest inhibitory activity (15.8 µmol / l) is a new compound which was named Terrestrimine (Song et al., 2014).

### Indirect action on SARS-CoV-2 by an immunomodulatory effect

Here we will focus on the immunomodulatory activity of four medicinal plants widely used in traditional medicine in Morocco (Bellakhdar, 1997; Skalli et al., 2019): garlic (*Allium sativum*), Ginger (*Zingiber officinale*), licorice (*Glycyrrhiza glabra*) and black pepper (*Piper nigrum*).

It has been shown that supplementation with garlic stimulates cell-mediated immunity (Beni and

Omidi, 2018) and that administration of alliin to mice with diet-induced obesity produces an anti-inflammatory effect by reducing or stabilising cytokine levels (Sánchez-Sánchez et al., 2020).

Furthermore, two clinical trials have demonstrated that regular consumption by healthy volunteers of tea containing five herbs, including ginger and licorice, increases the activity of NK immune cells (Bhat et al., 2010).

In another study, ginger administration to athletes for six weeks decreased plasma levels of the cytokines IL-1β, IL-6 and TNF-α (Zehsaz et al., 2014).

It was also demonstrated that administration of piperine, an alkaloid contained in black pepper, produces an increase in the number of leukocytes in the blood of BALB/c mice (Sunila and Kuttan, 2004). Moreover, the mouse's splenocytes exposed to piperine showed a proliferation of T and B cells and enhanced macrophage activation (Sharma et al., 2014).

### DISCUSSION

In this review, we have emphasised the fact that products of natural origin could be active against SARS-CoV-2 either for a preventive aim or for the treatment of the disease. The actions of these different natural products call upon different molecular mechanisms: direct action on the viral envelope, slowing down of viral replication by inhibition of proteases, blocking the entry of the virus into host cells by binding to viral proteins and enzymes involved in this mechanism, or by indirect action through an immunostimulant effect. Thus, as part of the research for effective treatments for COVID-19, molecules of natural origin (Figure 1) whose possible action against SARS-CoV-2 has been demonstrated in-vitro or in-silico are potential candidates for future antivirals. They constitute interesting and promising leads that must be explored and confirmed by clinical trials.

On the other hand, given that products of natural origin and particularly vegetal products, are very popular and widely used all over the world, especially Morocco, and given that infection with SARS-CoV-2 causes a drop in immunity by a decrease of T lymphocytes and an increase of pro-inflammatory cytokines (Qin et al., 2020; Chen et al., 2020), health authorities worldwide should consider the possibility of issuing formal recommendations for the use of certain plants whose safety has already been proven, for the prevention of the infection with SARS-CoV-2 following the model of some countries

like India (Ministry of Ayush , 2020). These recommendations should relate in particular to plants known to have a fortifying and immunostimulant effect, and target the vulnerable people.

## CONCLUSION

Since COVID-19 has affected millions of people worldwide and caused more than a million deaths, the world is in urgent need of an effective treatment. Medicinal plants, such as those from the traditional Moroccan pharmacopoeia, offer a promising, affordable and relatively easy alternative. Researchers and health authorities should focus more on using the scientific knowledge already acquired on the anti-SARS-CoV-2 and immunostimulant activity of natural products as a lead for the treatment and prevention of COVID-19.

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## Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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