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The Possible use of Some Moroccans Medicinal Plants for their Antiviral Activity against SARS-CoV-2- A Review

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***Abstract*—Until now, (13/09/2020), the Covid-19 pandemic caused by the novel coronavirus SARS-CoV–2, has infected more than 29 million people worldwide and is responsible for at least 920.808 deaths, Since the outbreak of the disease in for the first time in Wuhan, in China, on December 31, 2019. This pandemic has also several repercussions on the daily life of man, at the economic, social and psychological levels. The need to develop effective treatment against SARS-CoV-2 is the major objective of all countries, so far a hundred global laboratories are competing to produce a vaccine against Coronavirus, Russia has announced it has developed the first vaccine against the coronavirus named "Sputnik", in China researchers say they have already developed a test phase treatment would accelerate the cure and also temporarily immunize against Covid-19. Japan, USA, Australia, France, UK and Germany are also trying to find a vaccine against SARS-CoV-2 based on existing drugs (antimalarial drugs, anti-HIV drugs...). Bearing, no drug has been detected to treat 100% new coronavirus to date. Faced with this situation, medicinal plants in Morocco constitute an immense reserve of molecules that can have antiviral activities. Moroever, herbal medicine in Morocco has always been used in the field of traditional medicine, the WHO estimates that traditional medicine covers the primary health care needs of 80% of the world's population. Despite the development of the synthetic drug, the plant drug would generally be better tolerated by the body, thus allowing for prolonged treatments and minor side effects. Several compounds, such as flavonoids, from medicinal plants have been reported to have antiviral activities. The present study is aimed at employing bibliographic research in scientific databases on articles and thesis published in this subject, to screen phytochemicals from Moroccan medicinal plants targeting the SARS-CoV2 for identification of antiviral therapeutics. The results promise that some moroccan medicinal plant, can be developed into pharmaceutical drugs for the production of vaccin anti SARS-Cov-2.**

***Index Terms*— Antivral activity, coronavirus, Covid-19 pandemic, Moroccan medicinal plants, SARS-CoV–2.**

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I. INTRODUCTION

Detected in Wuhan city of China, at December 2019, the COVID-19 pandemic has rapidly spread around the world, causing more than 29 millions infections, more than half of them in the USA, Brazil and India, and more than 920.808 deaths so far.

In Morocco. The first case of imported COVID-19 was detected on 02/03/2020, while the first case of local transmission was detected on March 13, 2020. The number of confirmed cases has gradually increased, leading the country to implement social distancing measures, consisting of the closure of land, air and sea borders since 15 March 2020, the cessation of studies for all school and university levels from 16 March 2020, the cessation of prayers at the level of mosques since 16 March 2020, the progressive confinement of the population since 20 March 2020, which remains partial [1]. These measures likely led to a relative slowdown in the spread of the epidemic.

After the beginning of the reduction of confinement measures, epidemic activity was particularly important for the regions of Tangier-Tetouan-Al Hoceima, Fez-Meknes, Marrakech-Safi and Casablanca-Settat. These four regions account for 80% of confirmed cases on the national territory. Up to the date of writing of this article, a total of 84.435 cases of COVID-19 have been recorded in Morocco until 13/09/2020, or a cumulative contamination rate of 146.6 cases for. 100,000, compared to a global rate of 303.7 per 100,000. The number of deaths reached 1.553 with a fatality rate of 1.73%. Most of these deaths have occurred at the last five weeks[2].

The pandemic continues to progress on the national territory, the focal dynamic (in professional and family environments) remains predominant. However, attack rates, rate of progression, in addition to the increasing frequency of cases for which infectious contacts could not be identified, suggest community-based transmission[2]. With this alarming situation and the absence of a vaccine or anti-Covid-19 treatment, the search for active ingredients from medicinal plants remains a privileged avenue that can offer researchers a resource to explore for a possible treatment against SARS-Cov-2.

Morocco contains almost 400 species of aromatic and medicinal plants [3]. They are plants whose organs are capable of synthesizing plant drugs as secondary metabolites with medicinal properties. Distributed on known botanical families such as Mytraceae, Poaceae, Asteraceae, Fabaceae, Cypereaceae, Brassicaceae, Rosaceae, Lamiaceae, Apiaceae,

Caryophyllaceae, Renulaceae..., different plant species of these are known for their antioxydant, antimicrobial and antiviral effects for a long time[4,5]. Nature provides an immense reservoir of chemicals to develop drugs for the treatment of various diseases and infections. Indeed, natural compounds extracted from medicinal plants and their derivatives are used in traditional medicine to treat many infections, including viral infections [6], Research on herbal medicines is becoming more and more interesting and yielding encouraging results. So far, a good number of medicinal plants around the world or their constituents have shown potential antiviral activity [7]. The world has started exploring traditional medicines for the treatment of viral diseases, which are comparatively more economical, easily available and bear fewer chances of side effects and toxicity. In this line, *Nigella sativa* known in morocco as "Habba Sawda" showed significant inhibitory activity against hepatitis C virus (HCV) [8]. A few natural compounds expressed their antiviral power by inhibiting viral replication within the host cell or by others mecanisms [9,10].

In this fact, and due to the lack of adequate and in-depth research on the development of SARS-Cov-2 drugs from herbal products. It is proposed to explore the plant regne and look for phytocompounds that can be capable not only for the fight against SARS-Cov-2 by providing natural compounds for the development of new alternative antiviral drugs to synthetic drugs, but also to prevent viral infections. On the basis of the preceding discussion, this review aims to establish a current state of knowledge on Moroccan medicinal plants and/or their derivatives that may have antiviral activity against SARS-CoV-2.

II. MATERIEL AND METHODS

A literature search was conducted in the PubMed, Google Scholar and Web of Science in order to find the most recent published articles related to the keywords such as “SARS-COV-2”, “moroccaon medicinal plants”, “Coronavirus”, “COVID-19”, “antivral activity”, “antiviral plants”, and “Phytotherapy” until 13/09/2020. No language restriction was imposed in this article. Some of required information was searched using following websites: The Official Portal of the Coronavirus in Morocco (http://www.covidmaroc.ma/) and the World Health Organization (https:// www.who.int/). A brief description about the epidemiological situation of coronavirus in Morocco was presented in this review. Significantly important Moroccan medicinal plants with the most actifs compounds with antiviral potential, especially against SARS-COV-2, were classified and discussed properly by providing relevant figure. Moreover, this article represented an overall review about the in vitro, in vivo or in silico studies applications of plant-based substances on SARSCoV-2 or on other similar viruses.

III. RESULTS AND DISCUSSION

A. *Curcuma longa*

Curcumin or diferuloylmethane with chemical formula of (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-di one) (Fig 1) **Error! Reference source not found.**is a polyphenolic compound from *Curcuma longa* (In Moroccan arabic: الكركم, al-kourkoum, الخرقوم, lkharkoum), this component has been described to have several functions in preventing or treating diseases, including cancers and viral infections. It has also been demonstrated that curcumin is an antiviral compound, with activity against diverse viruses such as dengue virus (serotype 2) [11], herpes simplex virus [12], human immunodeficiency virus [13], Zika and Chikungunya [14] among others. Curcumin and its analogues have proved to be useful as HIV–1 integrase inhibitor [12,15]. Others results showed that curcumin and its new derivatives gallium-curcumin and Cu-curcumin have remarkable antiviral effects on replication of HSV-1 in cell culture [16].

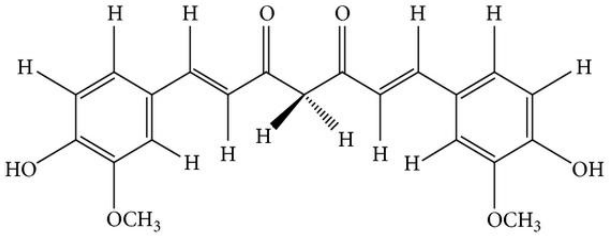

Fig 1: Chemical structure of curcumin

Curcumin has shown antiviral activity against several viruses. Its antiviral action against HIV has already been demonstrated by inhibition of HIV-1 LTR-directed gene expression, of HIV-1 LTR Tat-mediated transactivation, of HIV-1 and HIV-2 proteases and HIV-1 integrase and inhibition of Tat protein acetylation[17]. It has an action on HBV by suppression of HBV replication by increasing the p53 level, It's also responsible for the decrease of HCV replication by suppressing the Akt-SREBP-1 pathway and the inhibition of viral oncoproteins of E6 and E7 expression. The downregulation effect on the transcription of HPV and of Downregulation of JunD protein in HTLV-1-infected T-cell lines was also the result of the Curcumin[17]. The most important action of cumulin is the inhibition of haemagglutinin (HA), on of the major glycoproteins on the viral surface, and the main target antigen of the host immune system of Influenza A virus (IAV) inculding (H1N1 and H5N1) [18].

B. *Aloe vera*

Aloe vera (known in Morocco as الألوفيرا) is a medicinal plant cultivated for a long time in the Mediterranean region, North Africa, Canary Islands and Cape Verde. This plant has been used by people all over the world (Egyptians, Europeans, Moroccans, Indians, Chinese, etc.) for its internal and external benefits. The gel of *Aloe vera* has been used for healing and therapeutic purposes [55]. Lectins, fractions of *Aloe vera* gel, directly inhibited the cytomegalovirus proliferation in cell culture, perhaps by interfering with protein synthesis[19]. Several others ingredients in *Aloe vera* have been shown to be effective antiviral agent. Acemannan reduced herpes simplex infection in two cultured target cell lines [20]. The components include anthranol, barbaloin, chrysophanic acid, smodin, ethereal oil, ester of cinnamonic acid,

isobarbaloin, resistannol showed an antiviral activity but toxic at high concentrations [21]

An extract of *Aloe Vera* has been found to be effective against a broad range of viruses, especially causing the infections of the upper respiratory tract [22]. Anthraquinones like emodin and aloe-emodin isolated from *Aloe vera* exhibit good antiviral activity. Aloe-emodin (**Error! Reference source not found.**) possesses antiviral potential, reportedly inhibiting replication HHV-3 (human herpesvirus 3), herpes simplex Types 1 and 2, pseudorabies, influenza, human cytomegalovirus, and/or Japanese encephalitis virus [23-25]. and Human Immunodefeciency virus HIV[26]. It was identified as a potential interferon (IFN)-inducer demonstrated dose- and time-dependent actions on the inhibition of JEV (Japanese encephalitis virus) and EV71(enterovirus 71) replication via IFN signalling responses in mammalian cells [27]. Other anthraquinone derivatives like chrysophanic acid (**Error! Reference source not found.Error! Reference source not found.**) have demonstrated antiviral activity against hepatitis B/C, poliovirus, and HIV [24]. Electron micrograph examination of anthroquinone treated herpes simplex virus demonstrated that the envelopes were partially disrupted. Such results indicate that anthraquinones extract are directly virucidal to enveloped viruses. These actions may be due to indirect effect due to stimulation of the immune system. The anthraquinone (**Error! Reference source not found.**) aloin also inactivates various enveloped viruses such as herpes simplex, HHV-3 and influenza virus [25]. Others compounds derived from *Aloe vera such as* Catechin and Quercetin exhibited higher binding energetics to Main protease, Spike S protein and RNA dependent RNA polymerase (RdRp) in SARS-CoV–2, than the widely used hydroxychloroquine and other drugs used for treatment of COVID–19 [28].

It has also been reported that consumption of *A. vera* might be helpful to human immunovirus-infected individuals since it enhances the CD4 count and thereby improves the functioning of the immune system [26]. Compounds from *Aloe vera* like catechin and phillygenin showed significant interaction with protease and the quercetin displayed good binding with RNA-dependent RNA-polymerase of SARS-COV-2 [29]. This results implicate the antiviral activity of *Aloe vera* against SARS-COV-2.

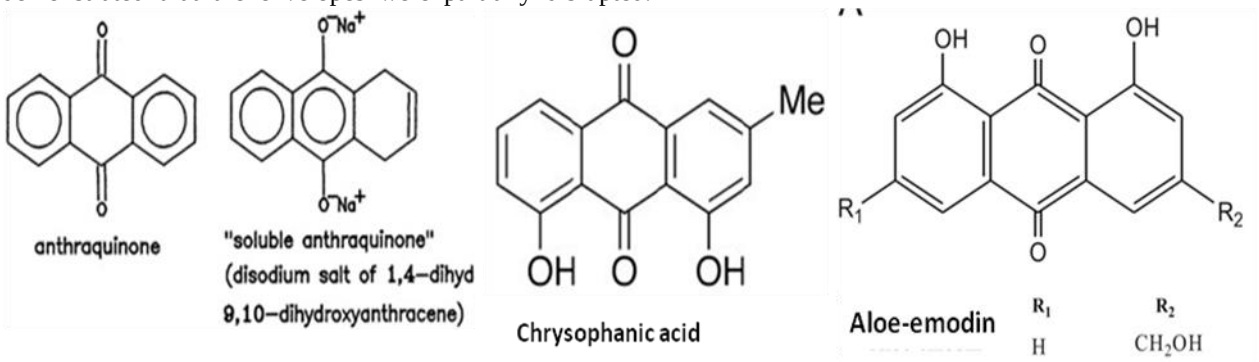

Fig 2: Chemical strucutre of the most actives compounds of Aloe vera

C. Silybum marianum

Silybum marianum or Milk thistle (known in Morocco as شوكة حمار, شوك الحليب, الخرفيش, شوك الجمل), This plant contains a compounds as Lignans, a class of natural products that possess diverse pharmacological properties and are known to be effective as antitumor, antioxidant, antibacterial and antiviral agents [30]. Silymarin, an extract of the seeds of milk thistle (*Silybum marianum*), is used as an herbal remedy, particularly for hepatoprotection. The main chemical constituents in silymarin are flavonolignans such as silybin A, silybin B and isosilybin A which have enhanced antiviral activity against HCV [31]. Moreover, Silymarin and its derivatives as attractive antiviral candidates against multiple viruses. The extract or molecular components appear to inhibit viral infection by targeting several steps of the viral life cycle either directly or indirectly [32]. Indeed, Sylimarin, Silybin or Silibinin Fig 3 may inhibit the HCV infection by the potentiation of the JAK-STAT antiviral signaling pathway, Inhibition of HCV-induced oxidative stress, as well as, the NS5B RdRp activity, NF-κB-dependent transcription, and T-cell receptor (TCR)-mediated proliferation, inhibition of NS5B polymerase activity and blocking viral entry and transmission or inhibition of HCV cell-to-cell spread and attenuation of HCV infection of PHHs[32]. Sylimarin is responsible for the inhibition of Dengue virus (DENV) and CHIKV replication and proteinsynthesis [33,34].

Since the genome of DENV and HCV are in the form of a positive-sense moncatenary RNA [35,36] like that of SARS-COV-2 which is a virus with a single strand positive RNA genome [37], In addition, the growth of CHIKV is also inhibited by chloroquine whose Anti-viral effects had already been demonstrated on SARS-COV-2 [38]. Interesting results were obtained in the study using the analysis of molecular docking and revealed Silybin to be the most promising inhibitor of the target proteins in SARS-CoV–2, significant binding energy with Silybin-main protease complex, with Silybin-S spike glycoprotein complex and with Silybin-RNA-dependent RNA-polymerase of SARS-CoV-2 in comparison to currently used repurposed drugs [29]. Moreover, recent studie stated that *Silybum marianum* have the highest effects on the most important receptors for SARS-Cov-2 which are ACE2,TMPRSS2 and GRP78 and my blocking these receptors and protect the body against the SARS-COV-2 infection [39].

Therefore we can suggest a possible exploitation of the antivral strategies of Sylimarine, Silybin or Silibinin, already mentioned, also against SARS-COV-2.

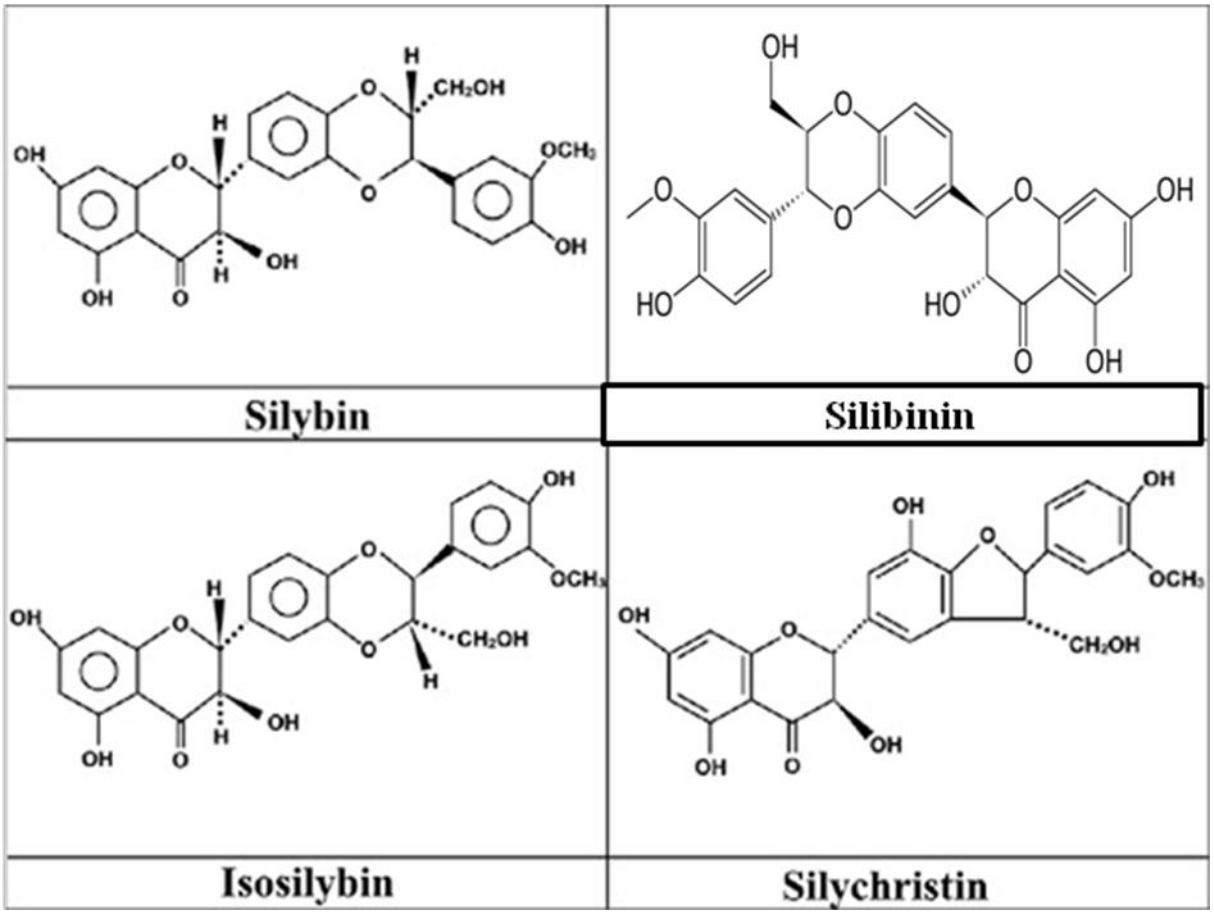

Fig 3: Chemical strucutre of the most actives compounds of *Silybum marianum*

D. Withania somnifera

Natural compounds derived from *Withania somnifera* (*known in morocco as lahw, bellahw or habb llahw)*[40], as Withaferin A, exhibited higher binding energetics with main protease in SARS-CoV-2 and spike protein/ACE2 than the widely used hydroxychloroquine and other repurposed drugs used for treatment of COVID–19 infection [29]. Other compound, the Withanolide A showed significant interaction with main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp) from SARS-CoV-2 [29]. Others research carried out by Khanal *et al*, concluded that Withanoloid Q was predicted to modulate the highest number of SARS-COV-2 proteins and had the highest druglikeness score. Moreover, Withanolide D and Withanolide G Fig 4 were predicted to have the better binding energy with PLpro (papain-like protease), Withanolide M with 3clpro (3C-like protease), and Withanolide M with spike protein in SARS-COV-2, based on binding energy and number of hydrogen bond interactions [41]. In other study it has been found that Withanoside V and Somniferine showed significant binding affinity for SARS-CoV-2 M^{pro}[42].

E. Argania spinosa

Argania spinosa (known in morocco as "الأركان "has been subjected to many pharmacological screenings. There is evidence of their wide spectrum of biological and chemical activities including antiviral as anti-HIV and antimalarial activities [43,44]. It has been shown that *Argania spinosa* contains five potent anti-coroavirus molecules Fig 5; procyanidin B1, kaempferol, betulinic acid, quercetin and luteolin, is commonly known as argan tree [45]. Indeed, Procyanidin B1 (PB1) known for inhibiting of infection by vesicular stomatitis virus and HCV pseudotype virus in Huh-7 cells, with 50% effective concentrations of 29 and 15 µM by inhibition of HCV RNA synthesis in a dose-dependent manner (RNA polymerase inhibitor)[46], showed s strong inhibitory effects on SARS virus infection with the CC_{50} value of 656.2 ± 36.7 µM [47]. Kaempferol showed significant inhibition of the cleavage activity of PLpro of SARS-COV-2 with IC_{50} of 16.3 µM[48]. Betutinic acid showed good antiviral properties in cell cultures infected with herpes simplex type I, influenza FPV/Rostock and ECHO 6 virus reproduction[49]. Similarly, quercetin showed efficient inhibitory activity against SARS-COV-2 Main protease with IC_{50} values was 23.8 µM[50]. It was also found that luteolin have been proven to be active against SARS-CoV.

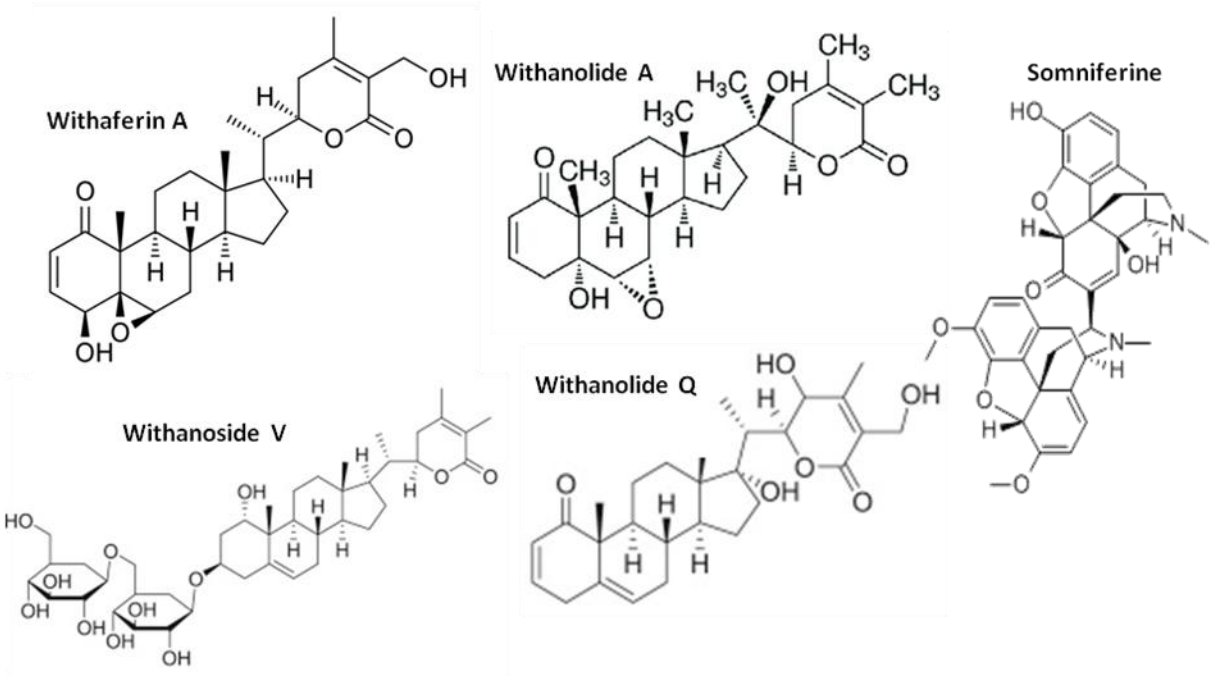

Fig 4: Chemical strucutre of the most actives compounds of *Withania somnifera*

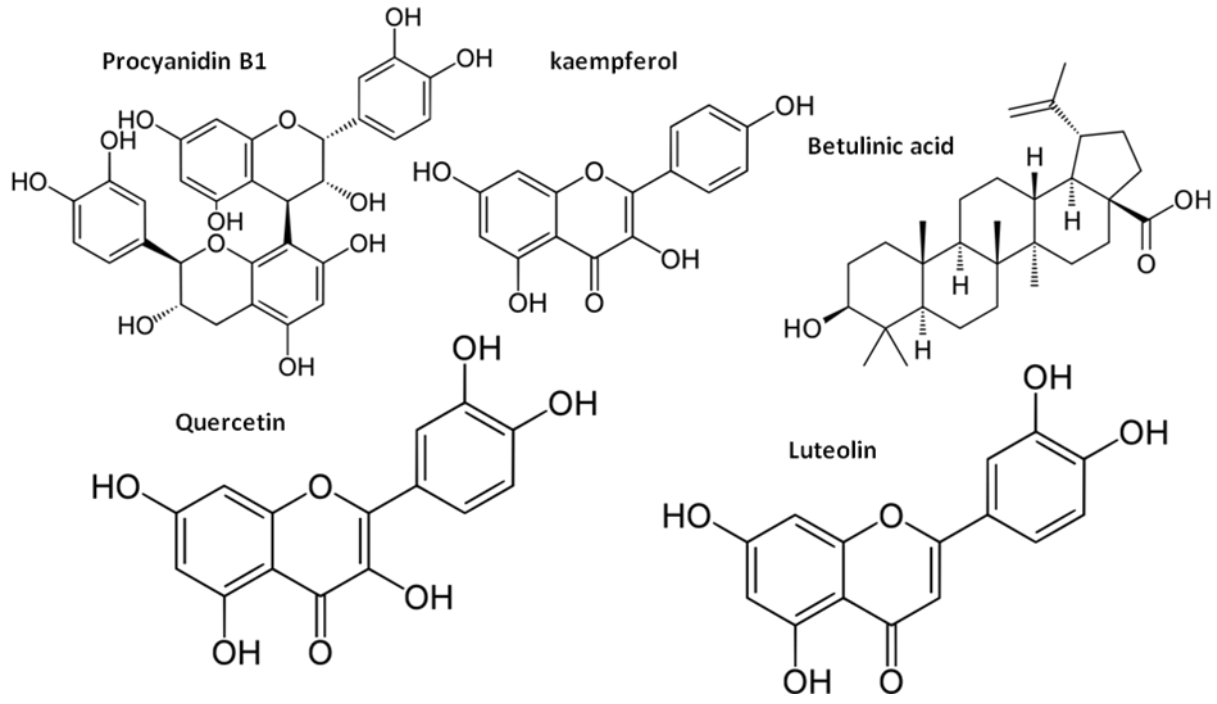

Fig 5: Chemical structure of the most potent anti-coronavirus compounds from *Argania spinosa*

F. Punica granatum

Punica granatum (الرمان in Morocco) is a fruit plant whose fruit's antiviral effects have been reported against clinically relevant influenza virus, herpes virus, poxviruses, and human immunodeficiency (HIV-1) virus [51-53]. According to Howell *et al.* [54]. It is possible that pomegranate juice and extracts could be potentially useful in inhibiting viruses transmitted via infected food products, bodily fluids, and so forth. Tannin from the pericarp of *Punica granatum* is an effective component against HSV-2. The tannin not only inhibits HSV-2 replication, but also shows stronger effects of killing virus and blocking its absorption to cells [55]. In the study conducted by Haidari *et al.* [51], the authors reported the presence of Punicalagin Fig 6 a polyphenol which has anti-influenza properties by suppression of replication of influenza A virus in MDCK cells, inhibition of agglutination of chicken red blood cells (cRBC) by influenza virus and is virucidal, inhibition of viral RNA replication [51].

This plant 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 [45]. Indeed, β-sitosterol exerts an inhibitory effect on the in vitro enzymatic activity of SARS coronavirus 3C-like protease[56]. Other finding reported that β-sitosterol had moderate efficacies against HBV replication[57]. The juice and liquid extract of *Punica granatum* contributed to rapid antiinfluenza activity [58].

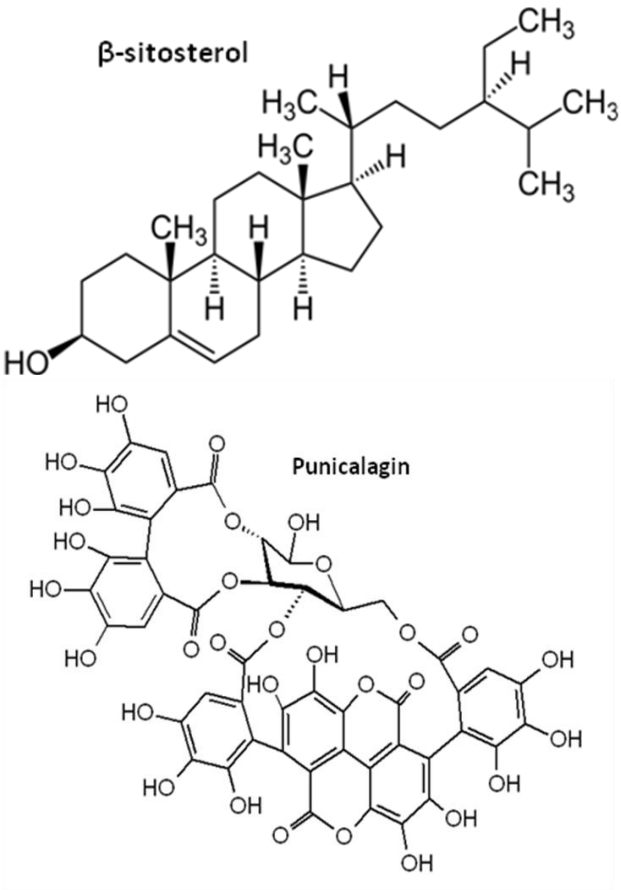

Fig 6: Chemical strucutre of the most potent anti-coroavirus compounds from *Punica granatum*

G. Ocimum basilicum

Ocimum basilicum or Basil, know in morocco as "Al-habaq=الحبق " contains mainly linalool and eugenol Fig 7 as the most active compounds, these two compounds are able to inhibit HSV-1 [59]. As regarding to SARS-CoV-2, several proteins have been identified which may serve as potential targets for chemotherapeutic intervention in COVID-19 disease. These protein targets include SARS-CoV-2 main protease pro (SARS-CoV-2 M), SARS-CoV-2 endoribonucleoase (SARS-CoV-2sp15/NendoU), SARS-CoV-2 ADP-ribose-phosphatase (SARS-CoV-2 ADRP), SARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp), the binding domain of the SARS-CoV-2 spike protein (SARS-CoV-2 rS), and human angiotensin−converting enzyme (hACE2) [60]. Eugenol have better docking properties with good docking scores with ADP ribose phosphatase of SARS-CoV-2 in order to −105.2 kJ/mol and normalized docking scores with Mpro (-93.2 kJ/mol) and endoribonuclease (-91,7 kJ/mol), this above data showed that this component can be considered viable chemotherapeutic agents for interaction with the SARS-CoV-2 target proteins. It has also been shown that linalool have an impact against coronavirus, the best docking score were showed to SARS-CoV-2 ADRP (DS_{norm} = −102.1kJ/mol) and to SARS-CoV-2 M_{pro} with DS_{norm} = −100.7 kJ/mol[60]. In the other hand, the SARS-CoV-2 spike protein serves to attach to angiotensin-converting enzyme 2 (ACE2) of the human cell to be invaded. The interface between SARS-CoV-2 rS and human ACE2 would be a promising target to prevent binding of SARS-CoV-2 rS to human ACE2 [61,62]. The good docking ligands with human ACE2, were observed by Eugenol (DS_{norm}=-88.4 kJ/mol) and Linalool (DS_{norm}=-87.84 kJ/mol) [60], all show docking preference to binding with ACE_2 and can subsequently prevent the SARS-COV-2 infection. Moreover, linalool has anti-inflammatory and antinociceptive activity, so there may be relief effects of COVID-19 symptoms[63].

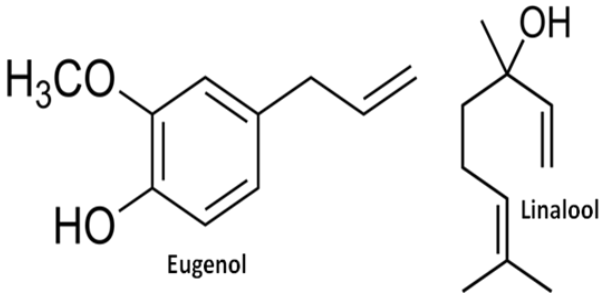

Fig 7: Chemical strucutre of the most potent anti-coroavirus compounds from Ocimum basilicum

H. 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 [45]. In the study conducted by Lin et al., [56] hesperetin was the most potent inhibitor of SARS-CoV 3CLpro, the results have demonstrated significantly inhibitory effects on SARS-CoV 3CLpro by hesperetin in the micromolar range. Particularly, the cell-based assay demonstrated that hesperetin (IC_{50}: 8.3 µM) could be potential inhibitors of SARS-CoV 3CLpro. In addition, hesperetin Fig 8 with a CC50 of over 2 mM were considerably less cytotoxic to Vero cells[56]. This phenolic compound dose-dependently inhibited cleavage activity of the 3CLpro in cell-free and cell-based assays. In the cell-free assay, the IC_{50} values were 60 µM for hesperetin[56]. Interestingly, *Mentha longifolia* can contain potential inhibitors against either PL^{pro} of SARS-COV-2 [45], this finding was consistent with a previous report indicating that hesperetin had an inhibitory activity also on Sindbis virus infection with an IC_{50} of 20.5 µg/ml [64]. Interestingly. *Mentha longifolia* contain potential inhibitors against either PL pro and/or 3CL pro [45].

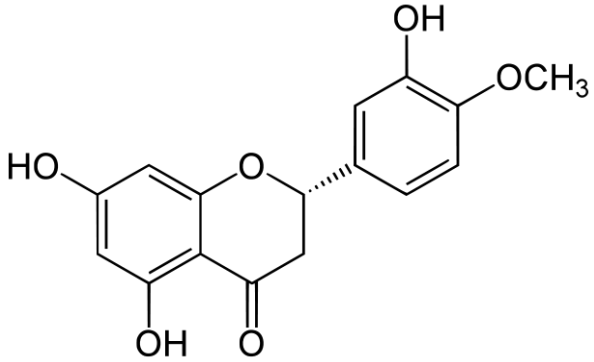

Fig 8: Chemical strucutre of hesperetin from *Mentha longifolia*

I. Portulaca oleracea

P. oleracea known in Morocco as " Rajla" contains five potent anti-coronavirus molecules, which are β-sitosterol,

quercetin, hesperetin, luteolin, and kaempferol [45]. A large number of studies conducted have reported that *P. oleracea* has antiviral activity against several types of viruses, in the study conducted by Li et al. [65], the authors reported that the water extract of *P. oleracea* (WEPO) inhibited the binding of influenza A virus to cells and exhibited good virucidal activity, significantly decreasing the viral load within 10 min to prevent viral infection. The production of circulating H1N1 and H3N2 was also suppressed [65].

These data indicated that WEPO has anti-IAV activity and might inhibit IAV at the entry stage of infection. Additionally, WEPO showed a significant anti-IAV activity in a dose-dependent manner. Other strains of IAV including A/California/07/2009 (H1N1), A/Perth/16/2009 (H3N2), and A/Brisbane/10/2007 (H3N2) were also inhibited by WEPO [65]. Moreover, pectic polysaccharide from *Portulaca oleracea* was deduced to be a pectin, which consisted of a predominant amount of galacturonic acid (GalA) with small amounts of galactose, rhamnose and Arabinose. This compound anti-HSV-2 activity. Furthermore, its anti-HSV-2 target was elucidated to be the step of virus penetration into host cells[66]. As regarding to quercetin which could inhibit both MHV and DENV-2[67], was capable to binfing with SARS-Cov 3CL protease and inhibing its proteolytic activity with an IC_{50} of 42.79 ± 4.95 µM [68]. Quercetin-3β-galactoside binds SARS-Cov 3CL protease and inhibits its proteolytic activity with an IC_{50} of 42.79 ± 4.95 µM [68]. Quercetin was also identified as a compound able to block SARS-Coronavirus entry into Vero E6 cells with EC50= 83.4 µM [69]. Quercetin inhibitory activity is also directed on SARS-Cov-2 virus entry, RNA polymerase, and on other necessary viral life-cycle enzymes [70].

J. *Zingiber officinale*

Zingiber officinale commonly called in Morocco as "الزنجبيل" or "سكينجبير" is a plant known for its medicinal properties as antiviral properties. A large number of studies conducted have reported that *Zingiber officinale* is a good, safe, low-cost and excellent natural source of different classes of natural compounds. In the study conducted by Amber et al., [71], the authors reported the presence of three sesquiterpene derivatives from *Zingiber officinale* which are ar-curcumene, β-sesquiphellandrene, α-zingiberene and β-bisabolene and two types of flavonoids flavan and 4, 6-dichloroflavan, all these compounds showed 50% inhibition against rhinovirus which are single strand positive RNA viruses. Gingerols are the major polyphenolic compounds in *Z. officinale* responsible for the pungent taste and have been reported to have application in the treatment of the respiratory disorder[72]. The gingerol has shown a good binding affinity towards COVID-19 main protease, and SARS-CoV 3 C-like protease[71,73], other study demonstrated the binding affinity of gingerol Fig 9 also to Nsp15 viral protein whic might play a key role in inhibiting SARS-CoV-2 replication [74].

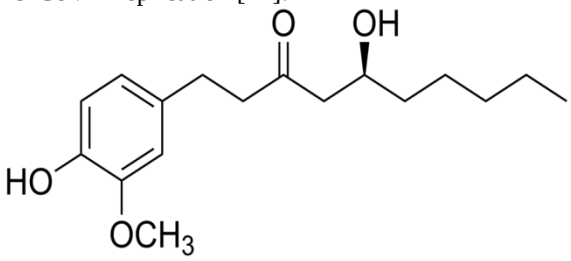

Fig 9: Chemical strucutre of gingerol

Moreover, the study conducted by Maurya *et al.*, reported that [75] Kadha, an Ayurvedic drink prepared with a combination of herbs and spices that are boiled usually in water and make a decoction including *Zingiber officinale* with its constituents: 6-gingerol, 6-shogaol, 6-paradol, Zingiberene, Bisabolene, 1-dehydrogingerdione, 6- gingerdione, 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 10- gingerdiol, Citral and Eucalyptol) [76,77]. Indeed, Regular consumption of ayurvedic Kadha may decrease the inflammatory response, boost the individual's immunity and reduce the risk of CoVs infection including SARS-CoV-2 [75]. Therefore, gingerl and 6-gingerol could act as a promising drug of choice to treat COVID-19. Moreover, Other constituents of Z. officinale must be invistigated for these possible antiviral properties against SARS-COV-2.

IV. Conclusion

In summary, this article focuses on the current state of knowledge on some Moroccan medicinal plants that may have antiviral activity against the SARS-COV-2 which causes the COVID-19 pandemic. 10 species found to be a source of more than 56 active ingredients which showed potential antiviral activity against SARS-COV-2 *in vitro*, *in vivo* or *in silico* (Table I**Error! Reference source not found.**). The phytochemical compounds identified in this article have shown an inhibitory effect either on the binding of the virus on the receptor of the host cell, or on the replication of the virus by acting on the replication enzymes or on the synthesis of the virus within the host cell. These phytochemical compounds can be an important effective alternative therapeutics for the treatment the prevention against COVID–19 pandemic. However clinical validation of these compounds is necessary.

Table I: Antiviral activities of the studied Moroccan medicinal plants

Medicinal plant name	The active compounds	The target virus	Antiviral action
Curcuma longa	Curcumin	Dengue virus-2 , HSV, HIV, Zika and Chikungunya [11-14]	HIV–1 integrase inhibitor [12,15]
		HSV-1	antiviral effects on replication of HSV-1 in cell culture [16]
			inhibition of LTR-directed gene expression, LTR Tat-mediated

	Curcumin and its derivates: Gallium-curcumin and Cu-curcumin.	HIV-1 and HIV-2	transactivation, HIV-1 and HIV-2 proteases and HIV-1 integrase and Tat protein acetylation[17].
		HBV	Suppression of HBV replication by increasing the p53 level[17].
		HCV	Decrease of HCV replication by suppressing the Akt-SREBP-1 pathway and inhibition of viral oncoproteins of E6 and E7 expression[17].
		HPV	The downregulation effect on the transcription of HPV and of Downregulation of JunD protein in HTLV-1-infected T-cell lines was also the result of the Curcumin [17].
	Cumulin	IAV inculding (H1N1 and H5N1)	Inhibition of haemagglutinin, on the major glycoproteins on the viral surface, and the main target antigen of the host immune system of IAV [18].
.. Leaves have three layers. The outer most layer consist of	Lectins	Cytomegalovirus	Interfering with protein synthesis[19]
	Acemannan	HSV	Reduction of HSV infection in cultured target cell lines [20]
	Aloe-emodin	HHV-3, HSV, influenza, human cytomegalovirus, JEV, EV 71, HIV [23-26].	Inhibition of replication via IFN signalling responses in mammalian cells as a potential interferon (IFN)-inducer [27].
	Chrysophanic acid	hepatitis B/C, poliovirus, and HIV	antiviral activity against [24].
	Anthraquinone	various enveloped viruses HSV, HHV-3 and influenza virus	Stimulation of immune system [25].
	Catechin, Quercetin		Inhibition of Main protease, Spike S protein and RNA dependent RNA

		SARS-CoV–2	polymerase (RdRp) [28].
	Catechin, Phillygenin		Interaction with protease of SARS-CoV–2 [29].
Silybum marianum	Flavonolignans as silybin and isosilybin A	HCV	antiviral activity [31]. Sylimarin is responsible for the inhibition of Dengue virus (DENV) and CHIKV replication and proteinsynthesis [33,34].
	Sylimarin, Silybin or Silibinin		Potentiation of JAK-STAT antiviral signaling pathway, Inhibition of HCV-induced oxidative stress, as well as, the NS5B RdRp activity, NF-κB-dependent transcription, and T-cell receptor (TCR)-mediated proliferation, inhibition of NS5B polymerase activity and blocking viral entry and transmission or inhibition of HCV cell-to-cell spread and attenuation of HCV infection of PHHs[32].
	Silybin	SARS-CoV-2	Inhibition of the Mpro, Spike glycoprotein complex and RNA-dependent RNA-polymerase of SARS-COV-2 [29].
	Silybum marianum extract		Blocking the receptors (ACE2, TMPRSS2 and GRP78) and inhibit the SARS-COV-2 infection [39].
Withania somnifera	Withaferin A	SARS-CoV-2	Inhibition of main protease in SARS-CoV-2 and spike protein/ACE2 [29].
	Withanolide A		Interaction with M^{pro} and RdRp [29].
	Withanoside V and Somniferine		binding affinity with M^{pro}[42].
	Withanoloid Q		Modulation of SARS-COV-2 proteins and the highest druglikeness score[41].
	Withanolide D and Withanolide G		Better binding energy with PLpro [41].
	Withanolide M		Inhibition of 3clpro [41]
Argania spinosa	procyanidin B1, kaempferol, betulinic acid, quercetin and luteolin [45]	SARS-COV-2	Anti-coroavirus molecules [47].
	Kaempferol		Inhibition of the cleavage activity of PLpro [48].
	Quercetin		Inhibition of Main protease [50].
	Luteolin		-------
	Betutinic acid	HSV-1, influenza FPV/Rostock and ECHO 6	Inhibition of the virus reproduction[49]
Punica granatum	Tannin from the pericarp	HSV-2	inhibits HSV-2 replication and shows stronger effects of killing virus and blocking its absorption to cells [55].
	Punicalagin	IAV	Suppression of replication of IAV, inhibition of agglutination of chicken red blood cells (cRBC) and inhibition of viral RNA replication [51].
	procyanidin B1, β-sitosterol, betulinic acid, quercetin, luteolin, and Kaempferol [45].	SARS-COV-2	Anti-coronavirus activities [45].
	β-sitosterol		Inhibition of enzymatic activity of 3C-like protease[56].

Ocimum basilicum L	Eugenol	SARS-COV-2	Inhibition of ADP ribose phosphatase of SARS-CoV-2, Mpro and endoribonuclease [60]. Good docking binding with ACE_2 which can inhibit the SARS-COV-2 infection. [63]
	Linalool		Inhibition of SARS-CoV-2 ADRP and to SARS-CoV-2 M_{pro} [60]. Good docking binding with ACE_2 and can subsequently prevent the SARS-COV-2 infection. [63].
Mentha longifolia	β-sitosterol, kaempferol, quercetin, luteolin and hesperetin [45].	SARS-COV-2	Anticoronavirus activity
	Hesperetin		Inhibition of cleavage activity of the 3CLpro and PL pro [45,56].
Portulaca oleracea	β-sitosterol, quercetin, hesperetin, luteolin, and kaempferol [45].	SARS-COV-2	Anticoronavirus activity
	Water extract of P. oleracea (WEPO)	IAV, H_1N_1 and H_3N_2	Inhibition of the binding of IAV to cells decreasing the viral load within 10 min to prevent viral infection[65]. Suppression of the production of circulating H_1N_1 and H_3N_2 [65]. Inhibition of IAV at the entry stage of infection in a dose-dependent manner [65].
	Pectic polysaccharide: galacturonic acid (GalA)+galactose, rhamnose and Arabinose.	HSV-2	Inhibition of virus penetration into host cells [66].
	Quercetin	SARS-COV-2	Blocking SARS-COV-2 entry into Vero E6 cells, inhibition of RNA polymerase, and other necessary viral life-cycle enzymes [69,70]. Inhibition of proteolytic activity of 3CL protease [68].
	Quercetin-3β-galactoside		Inhibition proteolytic activity of 3CL protease [68].
Zingiber officinale	Ar-curcumene, β-sesquiphellandrene, α-zingiberene, β-bisabolene, flavonoids flavan and 4, 6-dichloroflavan	Rhinovirus	----------
	Gingerols	SARS-CoV-2	Good binding affinity towards main protease, 3 C-like protease [71,73], binding affinity of gingerol also to Nsp15 viral protein (inhibiting SARS-CoV-2 replication)[74].
	Ayurvedic Kadha: 6-gingerol, 6-shogaol, 6-paradol, Zingiberene, Bisabolene, 1- dehydrogingerdione, 6-gingerdione, 10-gingerdione, 4-gingerdiol,6-gingerdiol, 10-gingerdiol, Citral and Eucalyptol [76,77].		Decrease the inflammatory response, boost the individual's immunity and reduce the risk of CoVs infection[75].

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