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Article

Approach of utilizing Artemisia herbs to treat covid-19

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Huge plethora of studies pointed out the importance of several Artemisia herb molecules as treatment for many diseases. Among these natural substances, some molecules are known to counteract fever, inflammation, blood clotting and oxidative stress. Furthermore, they are dotted with activities against different strains of viruses including the SARS-coronaviruses. For these beneficial properties, these medicinal herbs are deemed as a potential candidate for covid-19 pandemic.

Keywords: Artemisia. Therapy. Potential. Covid-19.

INTRODUCTION

The emergent SARS-CoV-2 belongs to the Coronaviridae family that causes severe acute respiratory syndrome with occasional pandemic features. The infection may lead to the coronavirus disease 2019 (covid-19), which manifests through fever, cough, nasal congestion, shortness of breath, loss of smell, headache and fatigue, among other symptoms. The progression of the pathology includes a harsh alveolar inflammation with the formation of a hyaline membrane. Vascular blood clots obtruding the exchange of respiratory gazes at the air-alveoli interface, in addition to lungs' epithelial cell damages leading to fatality due to acute respiratory distress syndrome (Badraoui *et al.*, 2020a; Gonzalez, 2020; Yuki, Fujiogi, Koutsogiannaski, 2020; Vetter, Eckerle, Kaiser, 2020). Yet, the medical care focuses on symptomatic therapy such as anti-inflammatory, antipyretics and mechanically assisted respiration. The severity of the disease is estimated dependently on the absence/presence of peculiar symptoms like the corporal temperature surpassing a threshold of 39°C and ansomia, thus the need for hospitalization (Wu *et al.*, 2020a; Wu *et al.*, 2020b; Badraoui *et al.*, 2020a). Because of the lack of specific and effective conventional drugs to eliminate covid-19, great efforts are spent for such concern.

Along the human history, medicinal herbs have been of great interest in treating various diseases (Pereira *et al.*, 2018; Badraoui *et al.*, 2020b; Akacha *et al.*, 2020). It has been reported that five species of the Artemisia genus (*A. maritima*, *A. fragrans*, *A. macrocephala*, *A. scoparia* and *A. vulgaris*) are already used by the Pakistan population to treat respiratory disorders. In such issue, Artemisia genus (from the Asteraceae family) is dotted with a large array of beneficial effects on health, and might be a potential candidate against covid-19 due to the major component namely artemesinin.

ANTIVIRAL POTENTIAL OF ARTEMISIA HERBS

Artemisia herbs contain hundreds of bioactive molecules including artemisinin and its derivatives that were effectively used to counteract malaria (Bora, Sharma, 2011; Kursat *et al.*, 2015; Lis, Kowal, 2015; Nigam *et al.*, 2019). These substances were actually reported to be potentially effective against several health problems (Kursat *et al.*, 2015; Saoudi *et al.*, 2017; Saoudi *et al.,* 2021). Interestingly, the screening of Artemisia extracts proved that many derivatives such as artemisinin, kaempferol and rutin, and whole aerial parts extracts of Artemisia species exert virucidal effects against diverse types of viruses, including coronaviruses (Arbab *et al.*, 2017; Brochot *et*

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al., 2017; Cheng *et al*., 2004; D'Alessandro *et al*., 2020; Han *et al*., 2015; Ivanescu, Miron, Corciova, 2015; Kim, Jeon, Ko, 2001; Lai *et al*., 2007; Li *et al*., 2005; Lubbe *et al*., 2012; Ma, Nakamura, Hattori, 2001; McCutcheon *et al*., 1995; Mitrocotsa *et al*., 2000; Romero *et al*., 2006; Sinico *et al*., 2005). The mechanism of action of these substances involves the inhibition of the virus attachment to its targeted cell, the expression of its proteins or its replication (Calderone *et al*., 1998; Efferth *et al*., 2008; Efferth, 2018; Wang *et al*., 2017). Some molecules, such as sterols, do prevent the targeted cell membrane lysis that is essential to the virus penetration (Abidi Ali Khan *et al*., 1991; Badraoui *et al*., 2021; Siddiqui *et al*., 2020). Other extracts restricted the horizontal cell to cell infection (Karamoddini *et al*., 2011; Saddi *et al*., 2007) and might be beneficial in covid-19 recovery, due to the antipyretic activity (Dib, Al Alaoui-Fares, 2019). In an animal experimental model, Shin (2017) proved that the oral intake of *Artemisia agryi* tea infusion improves the lungs' inflammation induced by lipopolysaccharide. This effect was accompanied with a relevant reduction in inflammatory markers in bronchial fluid (Shin *et al*., 2017). Bora and Sharma (2011) reported that the anti-inflammatory process by the plant metabolites could prevent the subsequent formation of the haylin layers, which disrupts the gaseous exchange in the alveolar-capillary membrane. In an experimental model, Kim (2005) showed that an extract from *A. capillaris* exerts a potent inhibitory effect on the production of inflammatory mediators such as nitric oxide and prostaglandin E2. Accordingly, other species from Artemisia genus showed similar effects by modulating inflammation and the immune response (Krebs, Omer, Omer, 2010; Messaoudene *et al*., 2011; Yoon *et al*., 2010). They also protected pulmonary epithelial cells through the inhibition of the oxidative stress process (Bora, Sharma, 2011). According to Lai and his colleagues (2007) the essential oil of *A. arborescens* facilitates the antiviral drug absorption and subsequentlyameliorates the conventional therapy. Several investigations proved the presence of anticoagulant molecules in Artemisia (Lv, Li, Zhang, 2017; Ryu *et al*., 2013; Shahriyary, Yazdanprast, 2009; Wang *et al*., 2011) that might counteract the covid-19 induced coagulopathy (Giannis, Ziogas, Gianni, 2020) and improve the blood-alveolar exchange of respiratory gazes (Figure 1). As part of our project devoted to the effectiveness and safety of the Tunisian medicinal herbarium, the usage of *Artemisia campestris* leaves by local the population to treat acute bronchitis was considered. In fact, we conducted a pilot- phase I clinical trial (from December 2018 to February 2019) in order to evaluate its effectiveness and safety. For this end, acute bronchitis' patients who were habituated to use *A. campestris* were treated either by oral administration of the infusion of the plant or the inhalation (snuffing) of 50 mg of its finely powdered leaves, as adjunct to conventional therapy. The Voucher specimen number of the used A. campestris is Bk11/96 and deposited in the Herbarium of the Institut des Regions Arides in Medenine, Tunisia. The phytochemical analysis of the plant, as assessed by mass spectrometric chromatography showed promising chemical compounds with potential health benefit (Akrout *et al*., 2001; Saoudi *et al*., 2017). Our results demonstrated that *Artemisia campestris* improves the wound healing of acute bronchitis, irrespectively of its viral or microbial origin. In fact, acutely diseased patients showed a relevant decrease in their bronchitis scaling score (BSS) following the intake of the infusion of 2 g of *A. campestris* leaves or the inhalation of 50 mg of its fine powder, twice daily for three successive days in comparison to placebo patients (who did not received the Artemisia treatment). The herb treatment significantly reduced the corporal temperature, blood C-reactive protein (CRP) content and the severity of respiratory distress symptoms, including dyspnea and cough. For example, the CRP concentration decreased from 28.75 ± 35.35 $mg \times L^{-1}$ and 28.03 ± 52.08 $mg \times L^{-1}$ to 7.74 ± 5.51 $mg \times L^{-1}$, and 10.81 ± 13.28 $mg \times L^{-1}$ respectively after the oral intake or the inhalation of *A. campestris*. However, there was substantial increase in CRP, from 16.20 ± 15.00 $mg \times mL^{-1}$ to 19.57 ± 35.92 $mg \times mL^{-1}$, in placebo. A complete resolution of cough was observed in 70%, 60% and 50%, respectively in patients treated by the herb product inhalation, or infusion, and placebo (unpublished data). Seemingly, the oral intake of Artemisia plants' tea- infusion is much common throughout the world, but some studies reported also its use through the inhalation of its (Braithwaite, Van Vuuren, Vijoen, 2008; Yang *et*

al., 2014). The induced phyto-therapy of the bronchitis might involve a bactericidal (Yang, Hu, Feng, 2015) and virucidal mechanisms (Arbab *et al.*, 2017; Calderone *et al.*, 1998; Efferth *et al.*, 2008; Effert, 2018). In addition, the utilization of *A. campestris* by the two routes was almost safe and did not present any toxic feature.

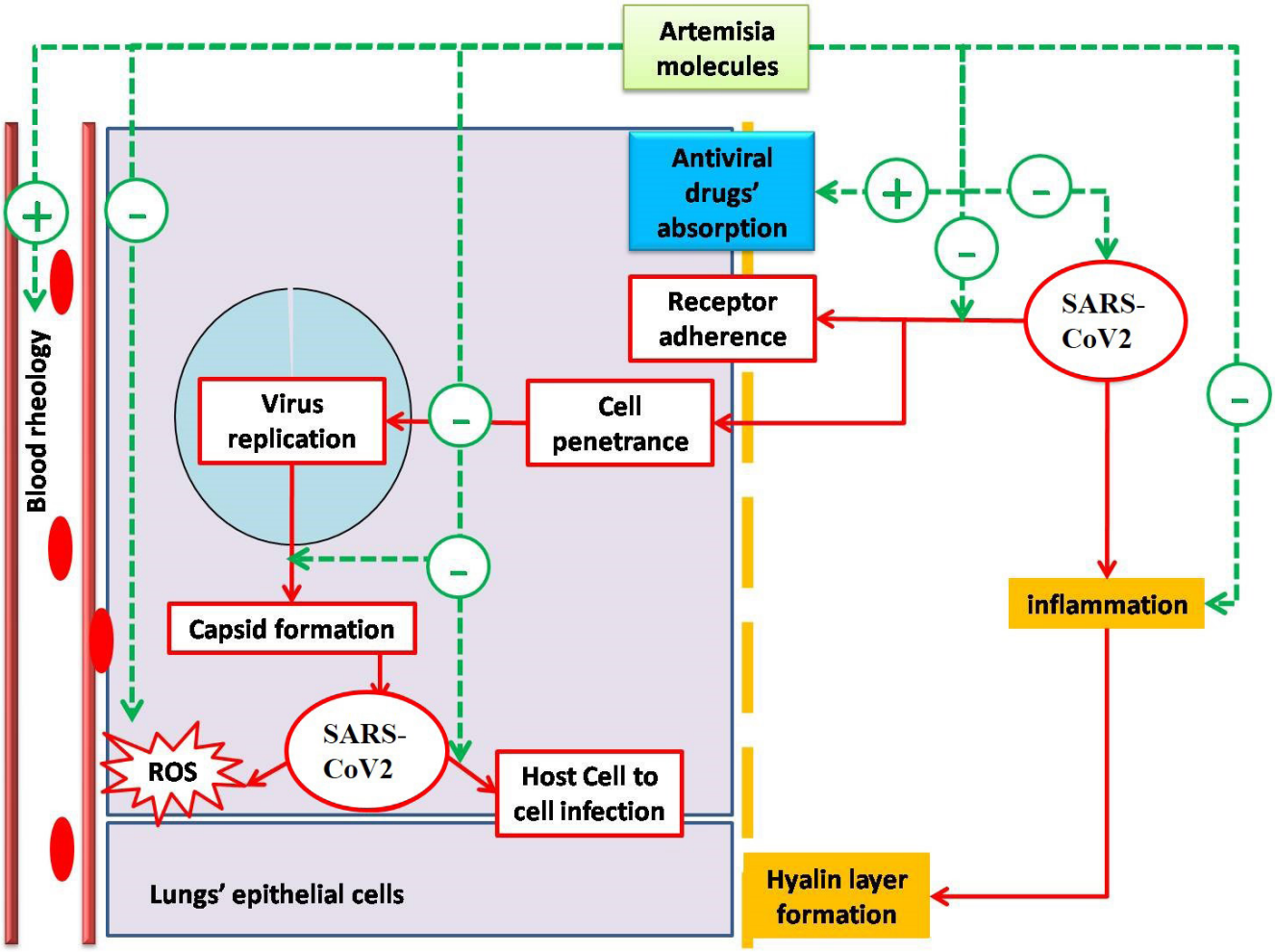

FIGURE 1 - Potential mode of action of Artemisia herbs' extract in curing covid-19. Artemisia herbs contain several compounds with antiviral activities and are sought as potential candidate to treat covid-19. These substances might inhibit viruses' replication, intracellular penetrance and inter-cells viral transmission. They also protect epithelial cells from the oxidative stress induced damages and prevent blood clotting in the vascular bed and the hyaline membrane formation which layout the gases' exchange- interface through their anti-inflammatory process. Furthermore, some Artemisia chemicals might facilitate antiviral drugs cellular absorption and ameliorate their curative effects.

Currently, many herbal molecules are being investigated for their potential to relieve the acute respiratory syndrome induced by the SARS-CoV-2. They are shown to inhibit the entry of the virus to the host cell, and its proteases that determine its 'survival' and replicative machinery. These molecules could also modulate the immune response associated SARS-CoV-2 infection (Chinsembu, 2020). In particular, Mpro inhibitors were extensively studied because of the importance of this enzyme in controlling the major phases of the proteolytic process governing the replication of the virus. This chemotrypsin -like protease cleaves the viral RNA- transcripted protein in eleven different sites (Biembrengut, De Souza, 2020; Kanhed *et al.*,

2021). Targeting this enzyme is sought as a specifically good approach in counteracting this pandemic. Thus, we specifically studied the virtual docking interaction of Artemisinin, one of the mostly represented sesquiterpenes' molecules in Artemisia genus, with the mean protease enzyme (M^{pro}) of the SARS-CoV-2. Our *in silico* probe revealed that Artemisinin potently bound to the M^{pro} site of action and established two to three conventional hydrogen bonds with affinity ranging from –5.2 to –8.1 kcal×mol^{-1}. Artemisinin interacts with the Cysteine 145 residue within the pocket region of the enzyme (Figure 2). The pharmacological and pharmacokinetic study of the molecule manifests a good oral absorption and bioavailability score (0.55) without any associated toxicity as assessed by the ADMET properties, which explains its ethno-pharmacological use.

While specific and concise experimental and clinical trials are still required to verify the importance of these herbal molecules in treating covid-19 patients (Kapepula *et al.*, 2020), the scientific culminating reports concerning this issue corroborate our findings and prompt the idea of possible use of Artemisia plants to fight the covid-19.

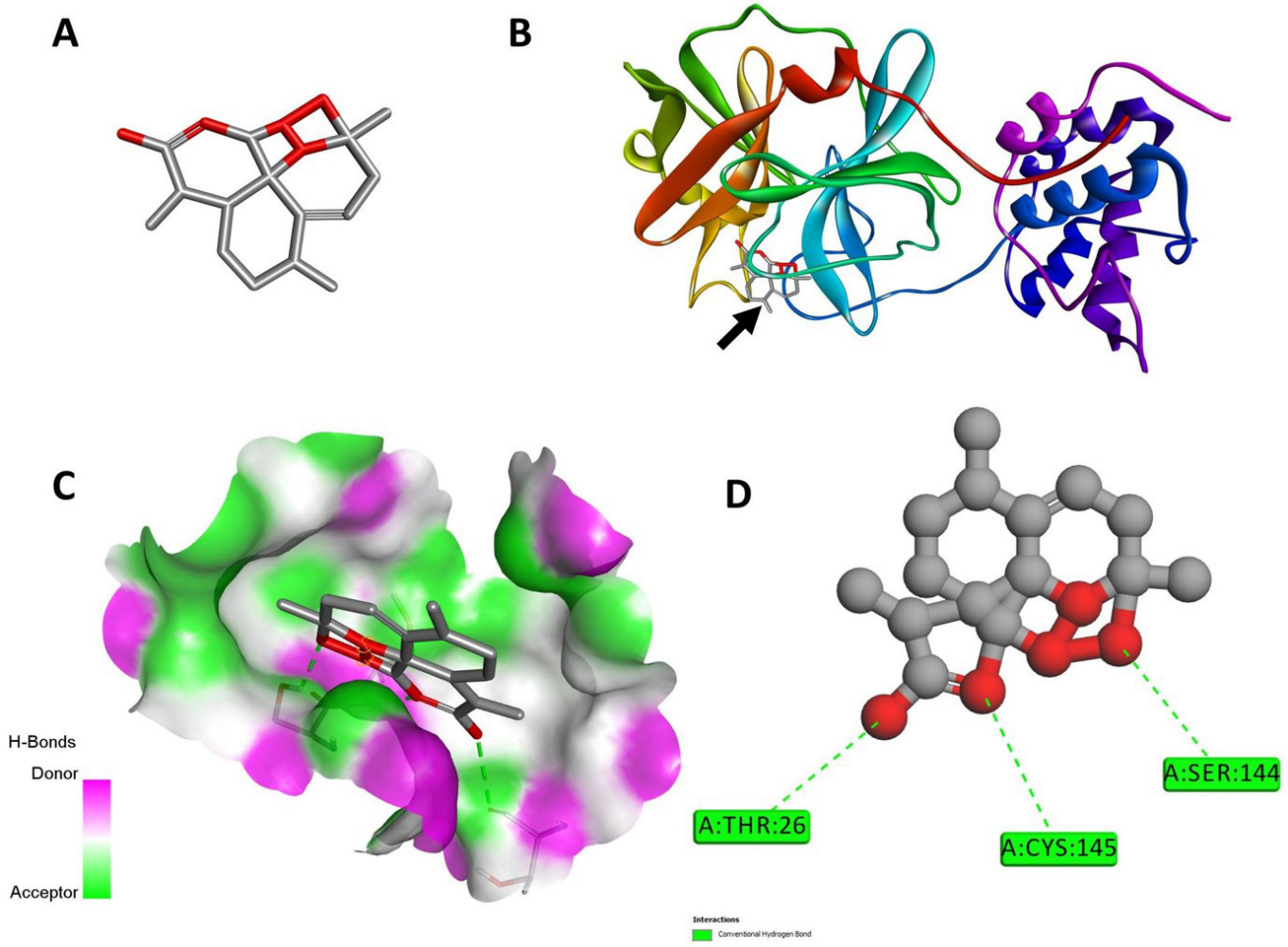

FIGURE 2 - The chemical structure of Artemesinin (A), illustration of artemesinin (arrow) docked to the ribbon structure of the targeted protein (M^{pro}) (B) and the established hydrogen bonds (C). (D) The bi-dimensional diagram of interaction within the ligand-receptor complex.

APROACH TO USE ARTEMISIA HERBS IN COVID-19 FIGHT

Many reported findings might plead in favor of the Artemisia herbs' consideration in fighting covid-19. In general, Artemisia species are safely utilized in traditional medicine, except for people suffering from hypersensitivity to their pollen and in cases of excessive intake where patients might develop anaphylaxis and renal disorders, respectively (Nauffal, Gabardi, 2016; Pablos *et al*., 2019; Tang *et al*., 2015; Aloui *et al*., 2010; Steven *et al*., 1997). To our knowledge, the inhalation route of the plant powder is the first reported one throughout the literature. Such pathway has the propensity to directly target the virus that exists in the whole airway, and to reach epithelia at the viral penetrating interface. In this regard, the molecules are suggested to exert all their potential (neutralizing the virus, inhibiting its penetrance to the host cell and its replication through repressing the virus proteases pathway) to inhibit the virus and the infected lung's inflammatory process and oxidative stress status; and to ameliorate the blood rheology and coagulability. Accordingly, the exploration of such administration route of the plant extract to counteract the disease might be a promising approach. To better ameliorate the effectiveness of Artemisia molecules, it is suggested to combine both the oral plant's infusion intake and its powder inhalation in order to neutralize/ inhibit the disseminated viron inside the organism. Herein, the plant aerial parts powder could be replaced by its aqueous maceration that might be pulverized to facilitate its inhalation; particularly in severe cases to prevent additional mechanical damages of infected epithelial cells. In the absence of experimental and clinical evidenced effects of the plant products against covid-19, its ethno-pharmacological application is still limited only to non-severe cases.

CONCLUDING RREMARKS

Artemisia herbs are very rich in biologically active substances. In particular, they show relevant antiviral effects. Within their worldwide large distribution and their non-toxic profile, except for hypersensitive peoples, they are sought as a good candidate to fight the covid-19 syndrome. We hope that deeper clinical investigations of such approach might help saving lives by management of SARS-CoV-2 inducing covid-19.

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