Essential oils a challenge against Covid-19: Review

Khadija BARY

Laboratory of Quality Control in Bio-Industry and Bio-Active Molecules, Faculty of Science, Chouaib Doukkali University, BP 20, El Jadida 24000, Morocco.

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ABSTRACT
Currently, the most pressing problem in the world is the SARS-CoV-2 pandemic with the increase in the number of newly infected and deceased patients. Scientists around the world are concerned about finding solutions to treat and prevent the SARS-CoV-2 virus all based on a safe and natural herbal derived medicine. Most essential oils contain molecules with antiviral activity and combine other interesting actions such as immune stimulation or an anti-inflammatory effect. Among the thousands of drugs in development or on the market, there may be effective treatments for the Covid-19 virus. Researchers have been sifting through the computer to identify those that could inhibit the essential interaction that SARS-CoV-2 has with the TMPRSS2 protein to enter our cells.

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1. Introduction:
In recent times, we can see a general public enthusiasm for natural and organic products. This development concerns not only the agri-food or cosmetics sector but also the use of traditional medicine. Although the popularity of traditional medicine has increased, most countries do not officially recognize it and therefore do not make resources available for research in this field. Aromatherapy is part of this new mode of organic consumption. Aromatherapy is part of this new mode of organic consumption. The diversification of news media around medicinal plants and the rise of self-medication have increased consumer interest in these products. They are especially looking for organic, effective and perfectly safe products.

At the end of December 2019, several cases of unexplained pneumonia occurred simultaneously in the city of Wuhan, in the Chinese province of Hubei, the 7th Chinese city with a population of 11 million. On 1 January, the Wuhan market was closed for sanitary reasons. The virus will be rapidly identified as belonging to the family Coronaviridae [1], related to the severe acute respiratory syndrome virus (SARS). The virus will later be known as severe acute respiratory coronavirus syndrome 2 (SARS-CoV-2), while the disease it causes will be known as COVID-19 for Coronavirus disease 2019 [2]. On 30 January, the WHO officially declared the infection a public health emergency of international concern. The disease is spreading rapidly outside China, and on February 25, for the first time, the number of new diagnoses outside China exceeds the number of diagnoses in China. WHO declares pandemic on March 11th, 2020. Europe is hit hard, with Italy being the most affected, followed by Spain, France and Great Britain. No specific antiviral treatment is currently available and no vaccine is available. The absence of conventional treatment, the development of efficient synthetic drugs or possible vaccines is subject to the temporality of research and validation protocols through clinical trials. Many antiviral molecules are being studied, including protease inhibitors, anti-HIV products, antimalarials, etc. So far, there is no consensus. Thus, the process that leads to the validation of a synthetic drug is very long and, while it may be relevant in normal times, it is failing in times of pandemic and generalized crisis [3]. In such a situation, very broad-spectrum solutions such as essential oils (EO), composed of dozens of molecules, seem relevant. This is what makes the success of essential oils in the face of "elusive" viruses such as herpes or flu. There are two types of viruses, naked viruses and enveloped viruses. Enveloped
viruses are protected by a lipid membrane allowing them to go unnoticed by the eyes of the immune system and to adapt better. Coronaviruses are enveloped viruses. To “attack” a wrapped virus, you need a fat-soluble active ingredient. Essential oils are fat-soluble.

2. Mechanisms for anti-viral action of essential oils:

Today, medicinal plants are widely studied in research centres around the world: there is hardly a university that does not have a unit dedicated to studying the therapeutic effects of extracts of medicinal plants especially their essential oils. It now appears that the most effective natural remedies in case of viral infection, are essential oils. Morocco has one of the oldest and richest traditions on herbal medicine and local people possess important data of medicinal plants. The researchers counted more than 600 plants used in herbal medicine in this North African country [4]. In addition, more than 60 plants are commonly used to treat and prevent respiratory diseases [4-10]. Studies on medicinal plants used for prevention purposes during Covid-19 were carried out in March 2020 in Morocco. Studies on medicinal plants used for prevention purposes during Covid-19 were carried out in March 2020 in Morocco [11-14]. Some of them have powerful virucidal effects because they are extremely reactive. This virtue requires that they be handled carefully and sparingly.

Many studies were limited to determining the presence or absence of an inhibitory action of EO on given Microorganisms (MO), while those seeking to elucidate their precise mechanisms of action and those of their components were rarer. Only recently have they started to develop. The basic concepts to be retained from the researches are firstly that the activity of EO is related to their lipophilic character, which allows their insertion into the lipid layers of the cell membranes, then that the biochemical structure associated with stereochemistry and functional groupings of active molecules appear to be the elements that condition their precise mode of action. There is no doubt that these are complex mechanisms in view of the diversity of aromatic molecules contained in an HE which not only possess their individual properties but also interfere with each other in order to act synergistically or modulate their activities. Overall the available data show that the anti-infectious activities of EO, can be divided into direct actions on MO and indirect actions on the individual carrying the infection in order to potentiate its own control mechanisms [15-16].

Modes of action:

It seems more complex to determine the antiviral mechanisms of EO since viruses need a host cell to multiply. There are, however, some studies on this subject. These have shown in vitro several modes of antiviral action varying according to the HE and the viruses on which they act, they consist of:

- Direct neutralisation before the virus enters the cell: at the capsid or envelope level, they act on the spatial conformation of their proteins or by substitution for a hydroxyl group of these proteins;
- A blockage of cells to adsorption and viral penetration: by competition thanks to the fixation of aromatic molecules to virus receptors;
- Intracellular action: by inhibiting viral replication after penetration;
- A destruction of the protective shell: the virus thus exposed becomes detectable by the immune system and immediately destroyed;
- An action on healthy cells: they acquire resistance to virus penetration, highlighted in clinical experiments and research in patients undergoing aromatherapy treatment.

Remarks: The liposolubility of HE allows them to penetrate the lipid envelope of the virus, they are therefore more active on the enveloped viruses than on the naked (more resistant). Moreover, they seem the most effective by dermal application and atmospheric diffusion [17-20].

The main active molecules belong to these biochemical families [21-23]:

- Phenols (ex: carvacrol, thymol, eugenol);
- Monoterpenols (ex: α-terpineol);
- Oxides (ex: 1,8 cineole);
- Aromatic aldehydes (ex: cinnamaldehyde);
- Terpenic aldehydes (in addition);
- The Ketones (cryptone).

The Covid-19 virus is also called SARS-CoV-2 because it is part of the same biological species as SARS-CoV, another coronavirus that caused the SARS outbreak in 2003. Following this outbreak, in vitro tests were carried out to test the effectiveness of certain essential oils against this coronavirus by inhibiting the replication of the virus in the cell. In fact, the Covid-19 treatment race involves knowing its structure and understanding how it works.

3. Structure and pathophysiology of Covid-19:

Coronaviruses are single strand RNA enveloped viruses. They infect a wide variety of species and are divided into four genera; α, β, γ and δ according to their genomic structure. Human coronaviruses such as 229E and NL63 are responsible...
for benign respiratory conditions and belong to the α coronavirus. In contrast, SARS-CoV, the Middle East respiratory syndrome coronavirus (MERS-CoV) and COVID-19-causing SARS-CoV-2 are classified as emerging β coronaviruses. Coronaviruses have four structural proteins; Spike (S), membrane (M), envelope (E) and nucleocapsid (N) (Figure 1). The receptor that allows the virus to enter the cells it infects is a molecule on their surface: the ACE2 enzyme. We can thus imagine ACE2 as a lock and TMPRSS2 as the key with which the virus can open it to enter. ACE2 is a protein widely expressed in the heart, vessels, intestines, lungs (especially in type 2 pneumocytes and macrophages), kidneys, testicles and brain. Its presence in these different organs seems to explain the variety of clinical patterns and complications related to COVID-19 [24]. SARS-CoV-2 penetrates the body’s cells by docking its surface protein Spike (S protein) to the host’s ACE2 receptors. These two structures were the first targets in the search for treatment against the novel coronavirus. But once attached to ACE2, the virus needs another cellular protein to continue its journey: TMPRSS2. It is an enzyme in the protease family that includes several structural domains. The main one, which is responsible for the proteolytic activity of the protein (serum protease domain), cuts the S protein of the virus in multiple places. This is a critical step for SARS-CoV-2 to enter the cell. TMPRSS2 also has a site located near the active site, which is called an exosite, and which plays a crucial role in helping the S protein to orient itself correctly before docking [25-26]. The entry of SARS-CoV2 into the cell lowers the ACE2 receptors, which therefore lose their capacity to degrade angiotensin II. It is this loss of expression and activity of ACE2 that may be responsible for the significant pulmonary inflammation and micro-thrombotic phenomena observed [27].

4. Essential oils: Is there a possibility of natural treatments for COVID-19?

To date, to our knowledge, only coronavirus resistance (SARS-CoV-2) results have been obtained through simulated mooring studies of organic compounds in garlic essential oil. The results showed that the 17 organosulfur compounds, which contain 99.4% garlic essential oil, have strong interactions with the amino acids of the ACE2 protein and the PDB6LU7 main protease of SARS-CoV-2. The strongest antiviral activity is expressed in allyl disulfide and allyl trisulfide, which account for the highest content in the garlic essential oil (51.3%). Interestingly, docking results indicate the synergistic interactions of the 17 substances, which exhibit good inhibition of the ACE2 and PDB6LU7 proteins. The results suggest that garlic essential oil is a valuable source of natural antivirus, which helps prevent coronavirus invasion into the human body [29].

A new essential oil, cajeput (Melaleuca cajuputi), has just distinguished itself by its potential to inhibit the proliferation of Sras-CoV-2 in the early stages of infection, according to new research (modelling by molecular docking). This work in Vietnam revealed that the cajeput-derived EO contains ten different compounds that strongly reduce the expression of the ACE2 protein (the key receptor for coronavirus entry into host cells) and protease PDB6LU7 (the most active enzyme in virus replication). The most active of these compounds would be terpineol, guaiol and linalool [30].

Researchers evaluated in silico (by computer) the action of eucalyptol (or 1.8 cineole) on proteinase (M proteinase/3CLpro), which would play a key role in the reproduction of the virus. As a result, its various binding capabilities with the Covid-19 protein, eucalyptol has serious therapeutic potential by acting as an inhibitor of this protein essential to the survival of Covid-19. In the development of a drug, these promising results require further research. In aromatherapy, this research confirms the potential of essential oils. Eucalyptol is found in many respiratory tropism essential oils such as Eucalyptus radiata, Eucalyptus globulus, Ravintsara, Cajeput or Niaouli [31].

The study, carried out by a team from the University of Calabria, concludes a “strong antiviral activity of Laurier Noble’s essential oil” against SARS-CoV. The essential oil from Laurus nobilis L. exhibited inhibition against SARS-CoV with an EC50 value of 120 µg/ml [32]. Another article highlighted the properties of Oregano (Origanum Vulgare) and Cinnamon [33].

Figure 1. 3D medical animation coronavirus structure [28].
The study of the composition of the essential oil of A. Herba-alba wild from Morocco indicates that the oil belongs to chrysanthenone/camphor/thujone/1,8-cineole, so rich in oxygenated monoterpenes which have been shown to be antifungal, antibacterial and antiviral [12].

These are essential oils of the monoterpenic alcohols groups (linalol, menthol, geraniol, borneol, terpineol, terpinene-4-ol), terpeneic oxides (1-8 cineol) and phenols (carvacrol, thymol, eugenol) and aromatic aldehydes (cinnamic aldehyde). Essential oils of this group such as Ravintsara Essential Oil (Cinnamomum Camphora CT cineol) are already used favorably in a number of viral pathologies such as influenza, herpes, shingles, infectious mononucleosis or chickenpox, in particular in terms of prevention.

A wide variety of antiviral compounds were found in 219 medicinal plants [34-37] belonging to 83 plant families. First and foremost, polyphenols, which contain multiple phenolic cycles, are classified as phenols, hydroxybenzoic acid, stilbenes, hydroxycinnamic acid, flavonoids, and lignans [38].

Polyphenols act against coronaviruses using a variety of mechanisms, including activation or inhibition of cell signalling pathways or the termination of the papain-like protease enzyme (PLpro) and 3-chymotripsin-like protease enzyme (3CLpro) [39,40]. The main protease (Mpro)/chymotrypsinlike protease (3CLpro) from COVID-19 represents a potential target for the inhibition of CoV replication due to its vital role in polyproteins processing necessary for coronavirus reproduction [41]. Some polyphenol compounds (30- (3-methylbut-2-enyl) -30, 4-hydroxyisolochocarpine, broussochalcone A, 4,7-trihydroxyflavane, broussocalcone B, papyriflavonol A, kazinol A, kazinol B, kazinol F, kazinol J, et broussoflavan A) isolated from Broussonetia papyrifera showed promising activity against SARS CoV. Higher efficacy against PLpro as observed by these compounds although the activity against Mpro or 3CLpro is not up to par. In particular, papyriflavonol A has an impressive activity against SARS CoV [42]. In silico analysis revealed that polyphenols can effectively inhibit SARS CoV-2 Mpro and RdRp [42, 43].

Flavonoid-type compounds, such as apigenin and quercetin, showed activity against SARS CoV virion particles by inhibiting Mpro enzymes with an IC₅₀ of 38.4 ± 2.4 μM and 23.8 μM, respectively [44-46]. Based on the in silico analysis, flavonoid compounds may terminate the Mpro activity of SARS CoV-2 [47-48].

In fact, many people wonder about the coronavirus and essential oils: can they really fight it? can they warn us about this? If so, which ones and how? ... Yes, essential oils can probably fight this new Covid-19 coronavirus, but scientists knowing very little about this infection makes it impossible to be categorical. Like all the publications you see on this subject, caution and hindsight are in order.

4. Conclusion:
The use of more rational experimental methodologies and the development of powerful computer tools will make it possible to identify antiviral compounds in silico, identified in essential oils, possibly able to block the entry of SARS-CoV-2 into our cells and which the most promising will soon be subjected to the first preclinical tests. However, the research is not good enough to be categorical. For this, the use of essential oils is still possible for any type of use subject to medical opinion. It is also important to follow the recommendations of the Department of Health and the government closely.

References:


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