JOURNAL OF ANALYTICAL SCIENCES AND APPLIED BIOTECHNOLOGY
An International Open Access, Peer Reviewed Research Journal

ISSN: 2665-8488
2021, Vol. 3, Issue 1
Pages: 1-6

Biotechnology

DOI: 10.48402/IMIST.PRSM/jasab-v3i1.23627

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.

ARTICLE INFO
Received November 14th,2020
Received in revised form February 1st,2021
Accepted February 2nd,2021

Keywords:
Aromatherapy,
Essential oils,
SARS-CoV-2,
Natural drugs,
Docking Simulation.

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

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

( ) Corresponding author:*
Tel.: + 212 6 25 628 783
E-mail address: barykhadija@gmail.com

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]**.

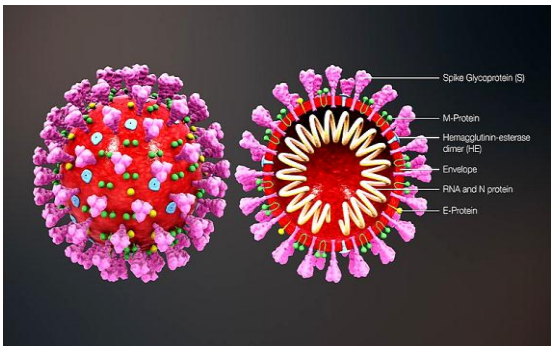

Figure 1. 3D medical animation coronavirus structure **[28]**.

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 organosulforous 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 anticoronavirus 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 EC_{50} value of 120 µg/ml **[32]**. Another article highlighted the properties of Oregano (*Origanum Vulgare*) and *Cinnamon* **[33]**.

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), terpenic oxides (1-8 cineol) and phenols (carvacrol, thymol, eugenol) and aromatic aldehydes (cinnamic aldehyde). Essential oils of this group such as Ravintsara Essential Oil (*Cinnamonum 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-hydroxyisolonchocarpine, broussochalcone A, 4,7-trihydroxyflavane, broussochalcone 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 **[41]**. *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 IC_{50} 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 molecules *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:

1. Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265-269.
2. of the International, C. S. G. (2020). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature microbiology*, *5*(4), 536.
3. Redouan, F. Z., Benítez, G., Picone, R. M., Crisafulli, A., Yebouk, C., Bouhbal, M., ... & Merzouki, A. (2020). Traditional medicinal knowledge of apiaceae at talassemtane national park (northern Morocco). *South African Journal of Botany*, *131*, 118-130.
4. Idm'hand, E., Msanda, F., & Cherifi, K. (2020). Ethnobotanical study and biodiversity of medicinal plants used in the Tarfaya Province, Morocco. *Acta Ecologica Sinica*, *40*(2), 134-144.
5. El-Hilaly, J., Hmammouchi, M., & Lyoussi, B. (2003). Ethnobotanical studies and economic evaluation of medicinal plants in Taounate province (Northern Morocco). *Journal of Ethnopharmacology*, *86*(2-3), 149-158.
6. Merghoub, N., Benbacer, L., Amzazi, S., Morjani, H., & El-Mzibri, M. (2009). Cytotoxic effect of some Moroccan medicinal plant extracts on human cervical cell lines. *Journal of Medicinal Plants Research*, *3*(12), 1045-1050.
7. Teixidor-Toneu, I., Martin, G. J., Puri, R. K., Ouhammou, A., Hawkins, J. A. (2017). Treating infants with frigg: linking disease aetiologies, medicinal plant use and care-seeking behaviour in southern Morocco. *Journal of ethnobiology and ethnomedicine*, *13*(1), 1-13.
8. Ainane, A., Khammour, F., Charaf, S., Elabboubi, M., Elkouali, M., Talbi, M., Ainane, T. (2019). Chemical composition and insecticidal activity of five essential oils: Cedrus atlantica, Citrus limonum, Rosmarinus officinalis, Syzygium aromaticum and Eucalyptus globules. *Materials Today: Proceedings*, *13*, 474-485.

9. Gharby, S., Asdadi, A., Ibourki, M., Hamdouch, A., Ainane, T., Hassani, L. A. I. (2020). Chemical Characterization of The Essential Oil From Aerial Parts of Lavandula rejdalii Upson & Jury, a Medicinal Plant Endemic to Morocco. *Journal of Essential Oil Bearing Plants*, *23*(6), 1422-1427.
10. Gourch, A., Zejli, H., Lfitat, A., Bousraf, F. Z., Yassine, E. L., Ainane, A., Taleb, M. (2020). Preventive impact of traditional medicine against covid-19. *Journal of Analytical Sciences and Applied Biotechnology*, *2*(2), 2-2.
11. Ainane, T. (2020). Moroccan traditional treatment for fever and influenza, similar to symptoms of coronavirus COVID-19 disease: Mini Review. *Journal of Analytical Sciences and Applied Biotechnology*, *2*(1), 2-1.
12. Asdadi, A., Hamdouch, A., Gharby, S., Hassani, L. M. I. (2020). Chemical characterization of essential oil of Artemisia herba-alba asso and his possible potential against covid-19. *Journal of Analytical Sciences and Applied Biotechnology*, *2*(2), 2-2.
13. El Alami, A., Fattah, A., Chait, A. (2020). Medicinal plants used for the prevention purposes during the covid-19 pandemic in Morocco. *Journal of analytical sciences and applied biotechnology*, *2*(1), 2-1.
14. Bary, K., & El Amraoui, B. (2020). Moroccan traditional medicine for the prevention and relief of corona virus covid-19 symtomes. *Journal of Applied Science and Environmental Studies*, *3*(4), 3-4.
15. Goetz, P., & Ghedira, K. (2012). *Phytothérapie anti-infectieuse*. Springer.
16. Elabboubi, M., Bennani, L., Ainane, A., Charaf, S., Bouhadi, M., Elkouali, M. H., Ainane, T. (2019). Treatment of mycoses by essential oils: Mini Review. *Journal of Analytical Sciences and Applied Biotechnology*, *1*(2), 1-2.
17. Astani, A., Reichling, J., Schnitzler, P. (2011). Screening for antiviral activities of isolated compounds from essential oils. *Evidence-based complementary and alternative medicine*, *2011*.
18. Wani, A. R., Yadav, K., Khursheed, A., Rather, M. A. (2020). An updated and comprehensive review of the antiviral potential of essential oils and their chemical constituents with special focus on their mechanism of action against various influenza and coronaviruses. *Microbial Pathogenesis*, 104620.
19. Boukhatem, M. N., & Setzer, W. N. (2020). Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. *Plants*, *9*(6), 800.
20. Nadjib, B. M. (2020). Effective antiviral activity of essential oils and their characteristic terpenes against coronaviruses: An update. *J. Pharmacol. Clin. Toxicol*, *8*(1), 1138.
21. Sahingil, D. (2019). GC/MS-olfactometric characterization of the volatile compounds, determination antimicrobial and antioxidant activity of essential oil from flowers of calendula (Calendula officinalis L.). *Journal of Essential Oil Bearing Plants*, *22*(6), 1571-1580.
22. Inouye, S., Uchida, K., Abe, S. (2006). Vapor activity of 72 essential oils against a Trichophyton mentagrophytes. *Journal of Infection and Chemotherapy*, *12*(4), 210-216.
23. Lo, C. M., Han, J., & Wong, E. S. (2020). Chemistry in Aromatherapy–Extraction and Analysis of Essential Oils from Plants of Chamomilla recutita, Cymbopogon nardus, Jasminum officinale and Pelargonium graveolens. *Biomedical and Pharmacology Journal*, *13*(03), 1339-1350.
24. Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*, *395*(10234), 1417-1418.
25. Ziegler, C. G., Allon, S. J., Nyquist, S. K., Mbano, I. M., Miao, V. N., Tzouanas, C. N., Zhang, K. (2020). SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*, *181*(5), 1016-1035.
26. Singh, N., Decroly, E., Khatib, A. M., Villoutreix, B. O. (2020). Structure-based drug repositioning over the human TMPRSS2 protease domain: search for chemical probes able to repress SARS-CoV-2 Spike protein cleavages. *European Journal of Pharmaceutical Sciences*, *153*, 105495.
27. Zou, X., Chen, K., Zou, J., Han, P., Hao, J., Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of medicine*, 1-8.
28. Ucar, F., & Korkmaz, D. (2020). COVIDiagnosis-Net: Deep Bayes-SqueezeNet based diagnosis of the coronavirus disease 2019 (COVID-19) from X-ray images. *Medical Hypotheses*, *140*, 109761.
29. Thuy, B.T.P., My, T.T.A., Hai, N.T.T., Hieu, L.T., Hoa, T.T., Loan, H.T.P., Nhung, N. .A. (2020). Correction to Investigation into SARS-CoV-2 Resistance of Compounds in Garlic Essential Oil. *ACS omega*, *5*(26), 16315-16315.
30. My, T.T.A., Loan, H.T.P., Hai, N.T.T., Hieu, L.T., Hoa, T.T., Thuy, B.T.P., Nhung, N. T. A. (2020). Evaluation of the Inhibitory Activities of COVID-19 of Melaleuca cajuputi Oil Using Docking Simulation. *ChemistrySelect*, *5*(21), 6312.
31. Sharma, A.D.; kaur, I. (2020). Eucalyptol (1,8 cineole) from *Eucalyptus* Essential Oil a Potential Inhibitor of COVID 19 Corona Virus Infection by Molecular Docking Studie . *s*, 2020030455
32. Loizzo, M.R., Saab, A.M., Tundis, R., Statti, G.A., Menichini, F., Lampronti, I., Gambari, R., Cinatl, J., Doerr, H.W. (2008). Phytochemical Analysis and *in vitro* Antiviral Activities of the Essential Oils of Seven Lebanon Species., *Chem Biodivers*, 5(3), 461-470.
33. Munhuweyi, K., Caleb, O. J., van Reenen, A. J., Opara, U. L. (2018). Physical and antifungal properties of β-cyclodextrin microcapsules and nanofibre films containing cinnamon and oregano essential oils. *LWT*, *87*, 413-422.
34. Kaushik, S., Dar, L., Kaushik, S., Yadav, J. P. (2021). Identification and characterization of new potent inhibitors of dengue virus NS5 proteinase from Andrographis paniculata supercritical extracts on in animal cell culture and in silico approaches. *Journal of Ethnopharmacology*, *267*, 113541.
35. Ryu, Y. B., Park, S. J., Kim, Y. M., Lee, J. Y., Seo, W. D., Chang, J. S., Lee, W. S. (2010). SARS-CoV 3CLpro inhibitory effects of quinone-methide triterpenes from Tripterygium regelii. *Bioorganic & medicinal chemistry letters*, *20*(6), 1873-1876.

36. Luo, W., Su, X., Gong, S., Qin, Y., Liu, W., Li, J., Xu, Q. (2009). Anti-SARS coronavirus 3C-like protease effects of Rheum palmatum L. extracts. *Bioscience trends*, *3*(4). 124.
37. Dai, J. J., Tao, H. M., Min, Q. X., Zhu, Q. H. (2015). Anti-hepatitis B virus activities of friedelolactones from Viola diffusa Ging. *Phytomedicine*, *22*(7-8), 724-729.
38. O'Keefe, S. J., Li, J. V., Lahti, L., Ou, J., Carbonero, F., Mohammed, K., Zoetendal, E. G. (2015). Fat, fibre and cancer risk in African Americans and rural Africans. *Nature communications*, *6*(1), 1-14.
39. Annunziata, G., Sanduzzi Zamparelli, M., Santoro, C., Ciampaglia, R., Stornaiuolo, M., Tenore, G. C., Novellino, E. (2020). May polyphenols have a role against coronavirus infection? An overview of in vitro evidence. *Frontiers in medicine*, *7*, 240.
40. Park, J. Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., Lee, W. S. (2017). Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. *Journal of enzyme inhibition and medicinal chemistry*, *32*(1), 504-512.
41. Lu, H. (2020). Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Bioscience trends*, *14*(1), 69-71.
42. Abdelmageed, M. I., Abdelmoneim, A. H., Mustafa, M. I., Elfadol, N. M., Murshed, N. S., Shantier, S. W., Makhawi, A. M. (2020). Design of a multiepitope-based peptide vaccine against the E protein of human COVID-19: an immunoinformatics approach. *BioMed research international*, *2020*.
43. Ghosh, R., Chakraborty, A., Biswas, A., Chowdhuri, S. (2020). Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors–an in silico docking and molecular dynamics simulation study. *Journal of Biomolecular Structure and Dynamics*, 1-13.
44. Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J. Y., Kim, D., Lee, W. S. (2010). Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. *Bioorganic & medicinal chemistry*, *18*(22), 7940-7947.
45. Kim, D. W., Seo, K. H., Curtis-Long, M. J., Oh, K. Y., Oh, J. W., Cho, J. K., Park, K. H. (2014). Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. *Journal of enzyme inhibition and medicinal chemistry*, *29*(1), 59-63.
46. Jo, S., Kim, S., Shin, D. H., Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of enzyme inhibition and medicinal chemistry*, *35*(1), 145-151.
47. Vijayakumar, B. G., Ramesh, D., Joji, A., & Kannan, T. (2020). In silico pharmacokinetic and molecular docking studies of natural flavonoids and synthetic indole chalcones against essential proteins of SARS-CoV-2. *European journal of pharmacology*, *886*, 173448.
48. Owis, A. I., El-Hawary, M. S., El Amir, D., Aly, O. M., Abdelmohsen, U. R., Kamel, M. S. (2020). Molecular docking reveals the potential of Salvadora persica flavonoids to inhibit COVID-19 virus main protease. *RSC Advances*, *10*(33), 19570-19575.