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Molecular Docking and Clinical Study of Inhibition of Phytochemical Compounds of *Nigella sativa*, *Matricaria chamomilla* and *Origanum vulgare L* on COVID-19 Mpro

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Abstract

Due to the high rate of infection reported in the new Coronavirus, in recent months, a lot of research has been done on the introduction of antiviral drugs. Recent studies have shown that inhibiting viral protease enzymes are highly effective in controlling infection caused by any type of virus. The aim of this study was to investigate the bioinformatics of inhibition of the new coronavirus protease enzyme by compounds in the essential oils of three medicinal plants. This is a descriptive-analytical study. For this bioinformatics analysis, the structure of compounds from PubChem database and the structure of COVID_19 protease enzyme were obtained from PDB database. Molecular docking was then performed by MVD software. The results showed that the site of interaction of the compounds in the protected area is enzymatic flap.

Keywords: Coronavirus; Bioinformatics; Molecular docking; Plant drug

Introduction

The Coronavirus infection is a disease associated with respiratory problems, which can lead to death from respiratory failure. About 210 countries and territories have been reported to be infected with the virus in the United States, China, South Korea, Italy, Spain, France, Russia, Turkey, Iran, etc. This article is dedicated to making an essential oil remedy for respiratory and inflammatory problems. Coronaviruses belong to the Coronaviridae family and appear just like spiked rings when observed through an electron microscope [1,2]. The surface looks with various spikes, which are helpful to attack and bind living cells. These are the viruses causing the simple common cold disease to severe illnesses like Middle East Respiratory Syndrome (MERS-CoV), Severe Acute Respiratory Syndrome (SARS-CoV). The source of these viruses is some animals including bats. The word coronavirus is a derivative of the Latin corona, which means crown or halo, that states to the typical look indicative of a crown or a solar corona around the virions [3-5]. These viruses are having a positive-sense single-stranded RNA genome (27 to 34 kilobases) and helical symmetry nucleocapsid. It should be noted that the outbreak of 2019 to 2020 in Wuhan, Hubei Province, China began in December 2019 when a new species of coronavirus was discovered on December 31, 2019. The World Health Organization has named the virus 2019-nCoV, which was later renamed by the International Committee for the Classification of Viruses as Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [6,7].

Methods

This research was a descriptive-analytical study. In order to obtain the 2 and 3 dimensional structure of the compounds, a PubChem database was used. The PDB database was used to obtain the complete structure of the protease enzyme. The structure mentioned in access number was received in the PDB database [8]. Also, in this study, 15 patients volunteered to use this combination with the steam treatment method and once a day, they received a steam treatment with a specific percentage of the combination of plants mentioned in this study.

Molecular docking

MVD automatically detects potential binding sites (cavities) using the cavity detection algorithm. To mechanize benchmarking, cavities within a 30x 30x30Å3 cube centered at the experimentally known ligand position were used. The cavities found by the cavity detection algorithm are actively used by the search algorithm guided differential evolution to focus the search, to that specific area during the docking stimulation. For each ligand docking, the best orientation for the ligand-protein complex was analyzed and hydrogen bonds were identified and labeled. The ligand energy was inspected and analyzed using MVD score, a linear combination of E-inter (steric, Vander Waals, hydrogen bonding and electrostatic interactions) and E-intra (torsion, sp2-sp2, hydrogen bonding, Vander Waals and electrostatic interaction) [9,10].

Steam therapy

Steam Inhalation is a method in which a patient is treated by receiving aqueous incense of medicinal plants. This type of treatment is more important for the treatment of diseases

related to the respiratory system and skin diseases, and due to the possibility of drug absorption from the capillary network of the nose, it is possible to treat many diseases with this method [11-13]. Inhalation, use of incense through the respiratory tract can be considered as one of the methods of entering and absorbing active plant substances or chemical molecules into the body [14].

Results

Docking Results

All of the studied compounds have been linked to 7 important amino acids in the protected position of the enzyme flap. Among them, the binding energy of three amino acids is very high. These three amino acids are Asparagine151, Aspartate153 and Phenylalanine294. According to the results in the **Table 1**, these compounds are connected to 18 residues, of which all compounds are connected to 7 residues, which we refer to the amount of binding energy. In Dithymoquinone, the amount of binding energy to Asn151 is -16, Asn156 is -11, Phe294 is -11, Ser158 is -3.3. In Farnesene, the amount of binding energy to Asn151 is -15, Asn156 is -9.2, Phe294 is -10, and Ser158 is -2.6. In Spathulenol, the amount of binding energy to Asn151 is -19, Asn156 is -10.5, Phe294 is -13, and Ser158 is -5.3. In Chamazulene, the amount of binding energy to Asn151 is -17.4, Asn156 is -11.6, Phe294 is -14.3, and Ser158 is -3.9. In En-yn-dicycloether, the amount of binding energy to Asn151 is -13.7, Asn156 is -16, Phe294 is -6.1, and Ser158 is -2.5. In Luteolin, the amount of binding energy to Asn151 is -20, Asn156 is -10, Phe294 is -6.6, and Ser158 is -2.3. In Thymol, the amount of binding energy to Asn151 is -19, Asn156 is -14.3, Phe294 is -6.9, and Ser158 is -6.1. In Geranyl_acetate, the amount of binding energy to Asn151 is -15.8, Asn156 is -10.3, Phe294 is -16, and Ser158 is -4.5. In Borneol acetate, the amount of binding energy to Asn151 is -19, Asn156 is -14, Phe294 is -12, and Ser158 is -3.6. In beta-Caryophyllene, the amount of binding energy to Asn151 is -14, Asn156 is -14, Phe294 is -13.7, Ser158 is -3.3. In beta-Bourbonene, the amount of binding energy to Asn151 is -19, Asn156 is -10, Phe294 is -14, and Ser158 is -1.9.

Compound Name	Total Energy	Ester Bond	Hydrogen Bond	Electrostatic Bond
Dithymoquinone	-97	-100	-7	0
Farnesene	-85	-90	0	0
Spathulenol	-82	-90	-2	0
Chamazulene	-71	-75	0	0
En-yn-dicycloether	-75	-69	0	0
Luteolin	-82	-90	-5	0
Thymol	-55	-56	-4	0
Geranyl_acetate	-86	-81	-5	0
Borneol acetate	-77	-74	-5	0
Beta-Caryophyllene	-72	-72	0	0
Beta-Bourbonene	-78	-80	0	0
Germacren D	-70	-75	0	0
Bicyclogermacrene	-71	-75	0	0
Caryophyllene oxide	-74	-75	-3	0
Carvacrol	-62	-60	-3	0

Table 1: The sum of the moldockscores resulting from the interaction of compounds and protease enzyme.

Clinical results

In a clinical trial, a combination of the plants studied in this study received a specific percentage of 15 volunteers who were mildly or severely infected with the coronavirus and who had symptoms of pneumonia, also severe cough and other symptoms of Covid_19. Some participants also took antibiotics and other medications to improve the symptoms of Covid_19. Finally, observations showed that in a few days after taking the drug, the symptoms of coronavirus disappeared in the body of patients receiving this compound and their coughs went away. Also, in patients with hypoxia, their oxygen levels increased with the use of this compound. In this article, we have included three cases of CT scans of patients.

Discussion

The use of herbal medicines in different countries is increasing day by day, and this is due to the proven effectiveness of these substances in human societies. Complementary therapy has been considered. Because corona affects the lungs, a drug that can enter the respiratory tract increases its inhibitory and therapeutic effects. Also, in this disease, pneumonia causes the severity of the disease. The aim of this study was to investigate the inhibitory effects of metabolites in the essential oils of three medicinal plants on corona virus protease. In this study, drugs were used that have previously been shown to have antiviral and anti-inflammatory effects and increase their immune system. Black seed plant with the scientific name of *Nigella sativa*. Thymoquinone and thymol are important compounds in its essential oil.

Conclusion

According to the results of the present study, the compounds in the essential oils of the three medicinal plants can communicate with the important amino acids present in the protected area of the enzyme to prevent the activation of the new coronavirus protease. Also, due to their essential oil, they

can enter the respiratory tract directly and have a double therapeutic effect.

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