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Original Research Article

Effect of spices and aromatic compounds on inhibit COVID_19 Mpro by docking analysis

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ABSTRACT

Coronavirus 2019 is a disaster in the 21st century and the lack of specific medications for prevention or treatment is a major need. In this regard, we conducted a conventional study to identify the main targets of coronavirus among spices compound. For this bioinformatics study, the ingredients structure was obtained from the PubChem database and the protease enzyme structure COVID_19 from the PDB database then molecular docking was performed by Molegro Virtual Docker (MVD) software. Based on the results, it could be concluded that the spices compounds interfere with the important amino acids in the enzymatic cavity to inhibit the protease enzyme virus. Regarding the binding energy among these compounds, the metabolites of curcuma longa, capsicum, zingiber has the strongest binding and inhibitory effect on the protease enzyme COVID_19. Therefore, these spices could be prescribed as a complementary treatment for patients with coronavirus infection in their food, but this study requires clinical investigation.

***Keywords*:** Coronavirus, bioinformatic, *in silico* screaning, secendary metabolite, drug target

INTRODUCTION

Coronaviruses are a large family of viruses, ranging from the common cold virus to the more serious diseases such as SARS, MERS, and CWID Fever, cough, and progressive respiratory failure, along with respiratory distress, are the most significant

manifestations of SARS infection. The high prevalence of hospitalization and mortality risk (15 %), in addition to the lack of preventive vaccines and treatment protocols, show the serious challenges of SARS in cases of global outbreak [1] . Their structure also contains a typical RNA genome. The novel coronavirus major protease (SARS-CoV-2 Mpro) play a crucial role during the disease propagation, and therefore SARS-CoV-2 Mpro indicates as a drug target for the drug discovery [2].

Spices

Spices have been with humans on food tables and flavorings for centuries. Spices with their various aromas and colors and their different medicinal properties have been the best seasoning for flavoring food. In addition to the unique flavor they gave to the food, the condiments also cured the diseases and illnesses of the consumers. Some types of spices are also used in the cooking and preparation of most foods, and many of us, without knowing it, enjoy their health, disease prevention or treatment benefits every day. The health effects of these additives have been identified in the past few decades by various studies including animal and laboratory studies. In these studies, the effects of spices on digestion, the effect of lowering blood lipids, anti-diabetic and lowering blood sugar, antioxidant properties, anti-oxidant effects Inflammation and anti-cancer have been reported [3]. Some spices include aroma compounds. In traditional medicine, herbs and aromatherapy, the use of essential oils and their aromatic compounds have long been known to manage various human diseases. Essential oil is a combination of very complex and natural aromatic compounds that are made by medicinal and aromatic plants as secondary metabolites. Essential oils are widely used in the pharmaceutical, cosmetic, health, food and agricultural industries due to their antibacterial, antiviral, antifungal, antipruritic, insecticidal, anticancer, neuroprotective, psychotherapeutic and anti-aging applications. They take. In addition, volatile perfume compounds include a diverse chemical class of organic compounds with low molecular weight with significant vapor pressure [4].

Molecular Docking

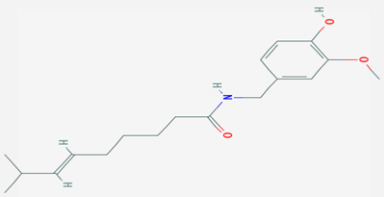
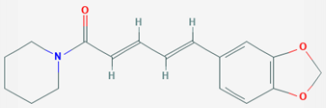
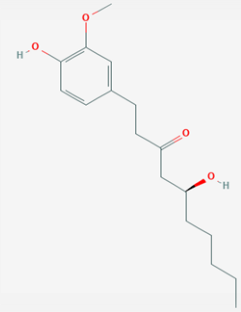
Molecular Docking is a subset of molecular modeling in bioinformatics. Docking can be used to predict the preferred orientation of one molecule over another as they bind together to form a stable complex. In other words, molecular docking is a key method in predicting the structure of the receptor

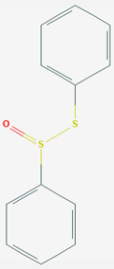
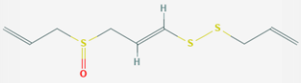
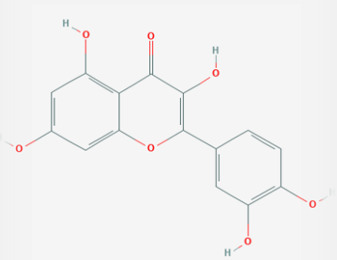
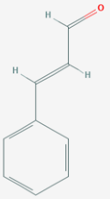
ligand complex in the process of discovering new leading drugs and compounds [5,6]. Searching for coronavirus enzyme inhibitors among plant secondary compounds can be one of the most effective ways to find the right drug. So far, much research has been done to identify coronavirus drugs, but little attention has been paid to plant secondary compounds [7]. Molegro Virtual Docker is a suitable software for predicting protein ligand interactions. In a simple graphical environment, this program has made it possible to prepare molecules, predict and investigate potential bonds with different ligands. Connections are displayed in a high quality 3D graphical environment. MVD, like other docking software such as AutoDock4 and AutoDock Vina, works successfully on hundreds of different proteins. There are three basic tasks any docking procedure must accomplish: characterization of the binding site; [1,2] positioning of the ligand into the binding site (orientation); and [3] evaluating the interaction strength for a specific ligand-receptor complex ("scoring") [8].

Data Collection

This study was a descriptive-analytical one. In this study, the interactions of secondary metabolites from commonly used spices and aromatic that have already been proven to have antiviral, antibacterial and anti-inflammatory effects are described in Table 1 and Table 2. For obtaining the 2-D and 3-D structures of the compounds, a PubChem database (https://pubchem.ncbi.nlm.nih.gov) was utilized. The PDB database was used to obtain the complete structure of the protease enzyme. The structure mentioned in access number 6lu7 was received in the PDB database at www.pdb.org.

Table 1. Name and 2D structure of the spices compound studied

No.	Secondary Metabolite	Spices	2D Structure of Secondary Metabolite
	Capsaisin	*Capsicum*	
	Piperine	*Piper nigrum*	
	Curcumin	*Curcuma longa*	
	Gingerol	*Zingiber*	

Diphenylthio sulfinate	*Allium sativum , Allium cepa*	
Ajoene	*Allium sativum*	
Quercetin	*Allium cepa*	
Cinamaldehyde	*Cassia*	

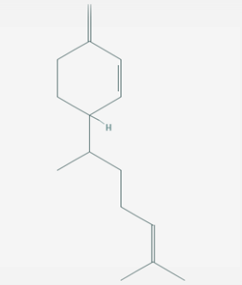
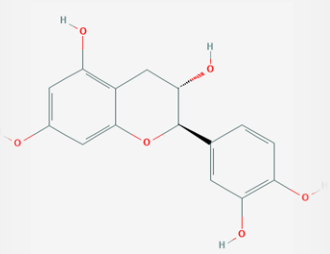
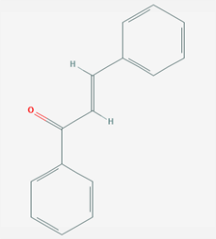
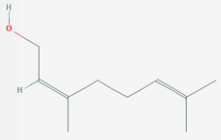
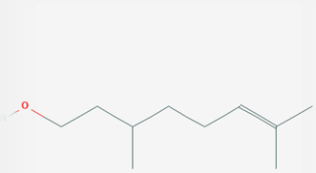
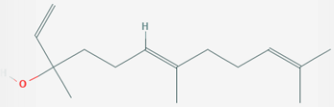
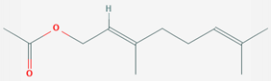
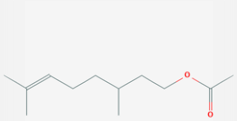
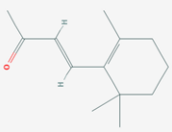
	Zingiberene	*Zingiber*	

Table 2. Name and 2D structure of the aromatic compound studied

No.	Secondary Metabolite	Source	2D Structure of Secondary Metabolite
	Catechin	*Camellia sinensis*	
	Chalcone	*Leguminosae, Asteraceae and Moraceae*	
	Nerol	*rose,flowery(Neroli, Lemongrass)*	

Citronellol	*Lemon*	
Nerolidol	*Fresh bark(Ginger, Jasmine)*	
Geranyl Acetate	*Floral*	
Citronellyl Acetate	*Rosa damascena Mill, Thymus*	
Beta_Ionone	*Viola*	

Molecular Docking

In this research, MVD was applied to analyze the molecular interaction between compounds and COVID-19 MPro. This software provides a 3D view of the interaction between compounds and the protease enzyme virus and the amino acids involving in the interaction. In the present study, all docking conditions including the interaction frequency, the study area of interaction, the protease enzyme and the rate of docking were considered to minimize error. Through the molecular docking, the frequency of interactions was determined 10, the distance of interaction area was determined 30 Angstrom. The hydrogen-electrostatic and van der Waals interactions was investigated in all active sites of the protein and the results were compared.

RESULTS

The results of this study indicate the strong interactions of compounds in the enzymatic flap conserved region. The results of software are summarized in Tables 3, 4 and 5. In the meantime binding to several amino acids due to their presence in the conserved region of the active site in all compounds is seen and plays a key role in enzymatic catalysis. The amount of binding energy of each compound is different from that of amino acids, and the result of all ester and hydrogen bonds is the total binding energy as shown in Table 3. All of the studied compounds have been linked to 10 important amino acids in the protected position of the enzyme flap. Among them, the binding energy of four amino acids is very high. These four residues are Asparagine 151, Aspartate 153, Gln 110 and Phenylalanine 294. According to Figures 1, 2 and 3, the software predicted 5 cavity to bind the ligands, which are green. These cavities are enzymatically protected areas for ligand binding. Of these five cavities, all the studied secondary metabolites were attached to the middle cavity. As a result by binding these compounds to the enzyme, the enzyme can't form its active state in the form of a dimer and the virus replication process will stop.

Table 3. The sum of the energies (MolDock Score) resulting from the interaction of compounds and protease enzymes

No.	Compound name	Total Energy (MolDock Score)	Ester Bond (MolDock Score)	Hydrogrn Bond (MolDock Score)	Electrostatic Bond
1	**Capsaisin**	-96	-92	-3	0
2	**Piperine**	-81	-79	0	0
3	**Curcumin**	-113	-110	-6	0
4	**Gingerol**	-100	-94	-5	0
5	**Diphenylthiosulfinate**	-76	-76	-0.1	0
6	**Ajoene**	-73	-68	-3	0
7	**Quercetin**	-78	-80	-3	0
8	**Cinamaldehyde**	-66	-61	-4	0
9	**Zingiberene**	-71	-71	0	0
10	**Catechin**	-81	-77	-6	0
11	**Chalcone**	-78	-77	-2.5	0
12	**Nerol**	-70	-64	-4	0
13	**Nerolidol**	-83	-83	0	0
14	**Geranyl Acetate**	-87	-80	-5	0
15	**Ionone**	-81	-80	-2	0
16	**Citral**	-71	-65	-4	0
17	**Citronellyl Acetate**	-80	-75	-4	0

Table 4. The amount of binding energy (MolDock Score) of amino acids in protease with compounds

AminoAsid	Arg	Asn	Asp	Asp	Cys	Gln	Gln	Ile	Ile	Phe	Lys	Phe	Pro	Ser	Thr	Thr	Tyr	Val	Val	Phe
Residue ID	105	151	153	295	156	107	110	106	152	8	102	294	293	158	111	292	154	104	157	112
Capsaisin	-3.7	-11.4	-12.4			-4.4	-8.8	-14.8	-4.3	-0.7		-14.5		-2.5	-0.9	-0.5		-7.1		
Piperine	-3.8	-12.7	-10.1	-0.5		-4.7	-4.5	-14.4	-4.1	-2.7		-5.9			-1.4		-0.3	-9.2		
Curcumin	-1.9	-19.5	-12.1	-4.4	-0.7	-2.0	-12.5	-8.2		-5.4		-23.2	-0.3	-8.2	-5.3	-1.2		-3.4		
Gingerol	-4.7	-16.3	-8.6	-0.9		-6.9	-11.9	-12.6	-5.3	-4.1		-12.8		-3.2	-2.0	-1.4		-5.9		
Diphenylthiosulfinate	-4.1	-16.5	-8.4			-3.9	-5.4	-12.3	-5.4	-3.9		-6.2		-2.4	-0.8			-5.4		
Ajoene		-13.6	-6.7	-1.7			-2.6	-0.9	-4.4	-4.2		-10.7		-2.9	-5.6	-1.9		-1.7		
Quercetin	-4.2	-19.3	-8.4		-0.8	-7.0	-9.8	-14.2	-5.4	-2.4	-0.4	-6.0		-3.6	-0.7			-6.2	-0.4	
Cinnamaldehyde		-17	-8	-3.7			-1.2		-5	-3.6		-8.7		-2.7	-8	-4.5				
Zingiberene		-12.8	-12.5			-3.4	-6.3	-9.1	-6.0	-4.0		-10.5		-0.7	-1.0		-0.3	-1.8		
Catechin	-6.5	-16.9	-6.5			-4.3	-10.1	-14.8	-2.5	-3.1		-4.3		-5.8	-0.8			-7.3		
Chalcone	-3.9	-18.7	-10.1	-0.3		-3.1	-4.5	-10.8	-6.2	-4.9		-3.9		-5.8	-0.8			-5.4		
Nerol		-16.6	-1.9	-1.3			-3.5	-3.3	-1.9	-3.9		-8.4		-0.9	-8.8	-0.4		-1.1		-0.4
Nerolidol	-4.4	-15.5	-10.6		-0.4	-1.9	-5.5	-9.6	-6.3	-1.9		-6.1		-2.3	-0.7			-5.7		
Geranyl Acetate		-17.4	-10.9	-3.4			-2.6	-1.0	-6.0	-3.2		-14.4		-4.4	-5.8	-5.6		-1.1		
Beta_Ionone		-19.2	-11.3	-2.7	-0.3		-1.9	-0.4	-7.4	-2.5		-16.6		-4.1	-6.1	-5.3		-0.4		
Citral		-11.8	-11.6	-2.0	-0.6		-3.0		-7.6	-3.1		-16.2		-3.4	-1.6	-1.3				
Citronellyl Acetate		-15.7	-6.2	-2.6			-6.6	-2.6	-3.5	-1.6		-14.7		-2.4	-4.5	-5.4		-1.3		

Table 5. The amount of energy (MolDock Score) of hydrogen bind in compounds with water

Water	HOH 408	HOH 417	HOH 440	HOH 456	HOH 463	HOH 479
ID	7	16	39	55	62	78
Capsaisin		-4.6	-2.9	-0.7	-3.5	-3.9
Piperine	-0.9	-2.0	-3.2		-2.2	-3.6
Curcumin	-1.5	-3.6	4.2	-3.5	-0.6	-0.6
Gingerol	-3.5	-1.2	-5.4	-0.4	-2.9	-0.7
Diphenylthiosulfinate	-0.7	-4.6	-2.4		-5.2	-1.3
Ajoene	-3.8	-1.4		-0.4	-1.4	
Quercetin	-1.8	-6.4			-3.6	-6.0
Cinnamaldehyde	-1.2	-1.3	-2.9		-1.3	
Zingiberene	-0.7	-1.8	-1.9		-2.0	-0.7
Catechin	-0.4	-3.9	-5.3		-3.1	-3.8
Chalcone	-1	-3.6	-3		-2.3	-1
Nerol	-2.3	-1.7	-4.9		-1.5	
Nerolidol	-2.9		-2.1		-2.5	-1.9
Geranyl Acetate	-0.9	-0.4	-2.2	-0.7	-1.1	
Beta_Ionone	-1.3	-1.1	1.7	-0.6	-1.6	
Citral	-1.1	-2.6	0.4	-1.1	-0.6	
Citronellyl Acetate	-0.9	-5.1	-2	-0.6	-2.8	

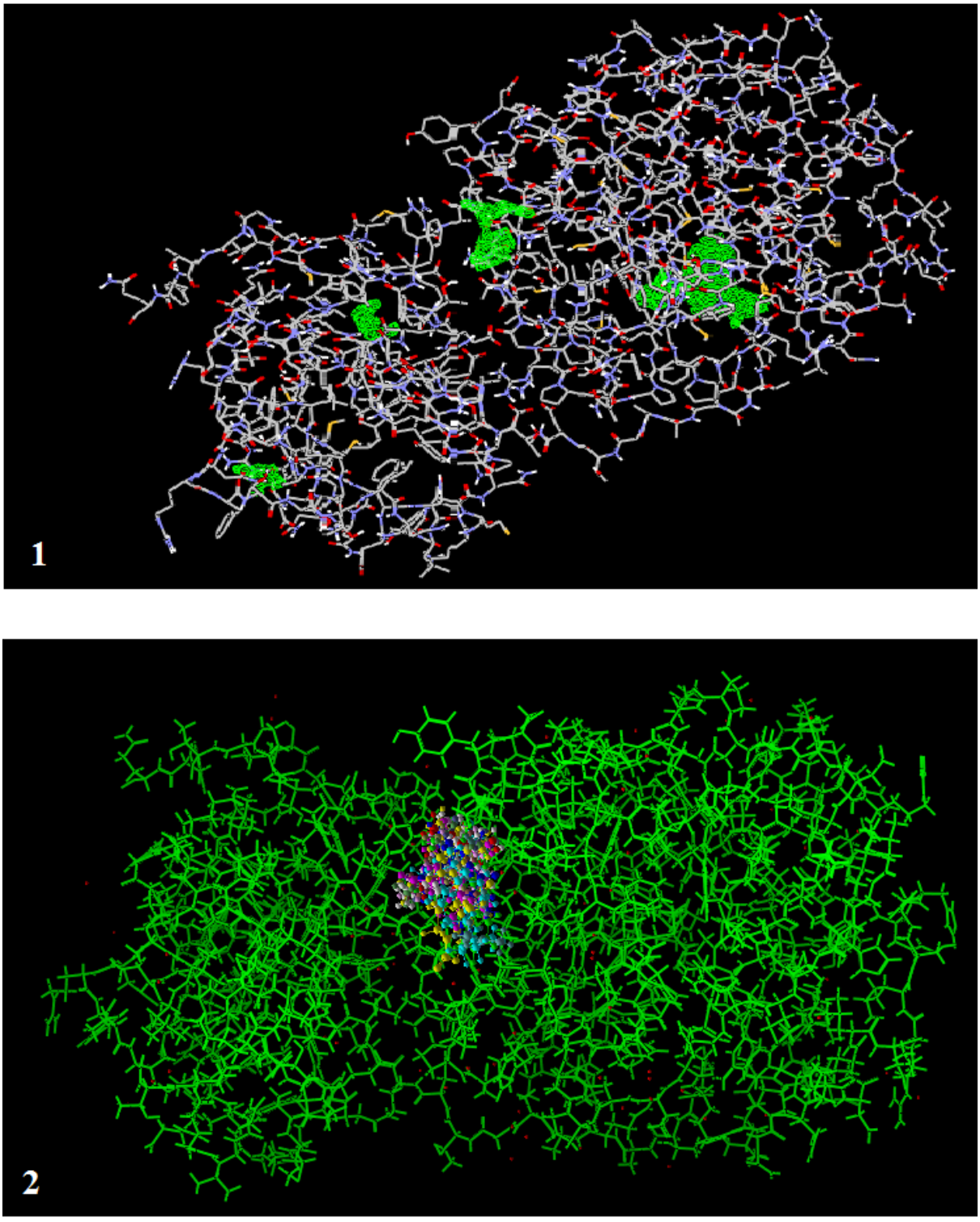
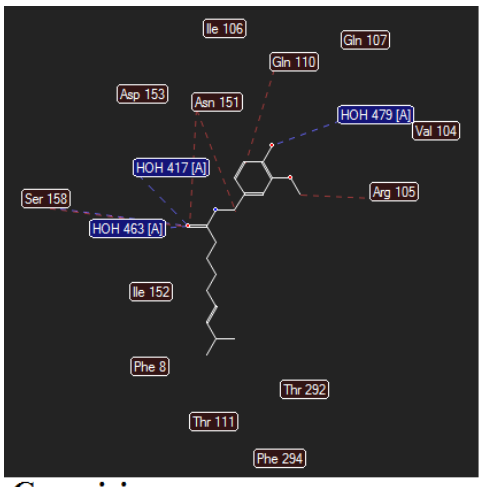
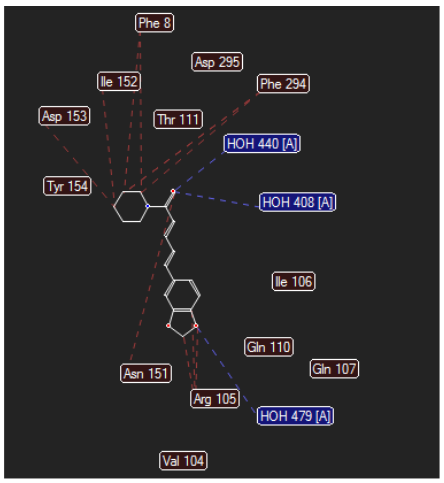


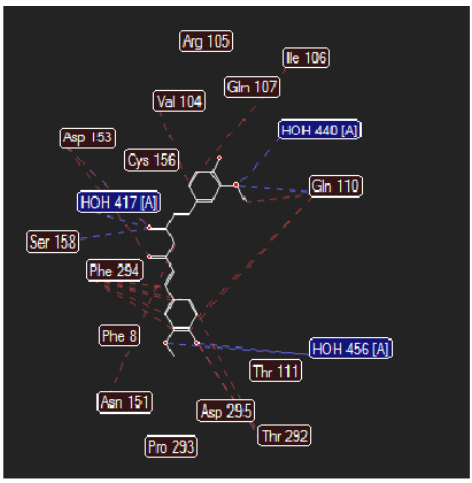
Figure 1. Detect 4 cavity for connecting drugs 2: Interactions between the compounds and COVID_19 protease are put into the middle cavity of the protease virus.



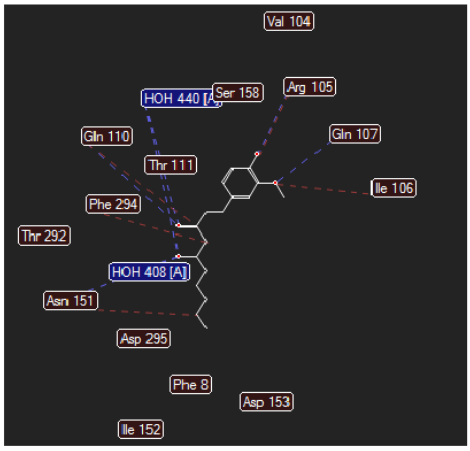
Capsaisin



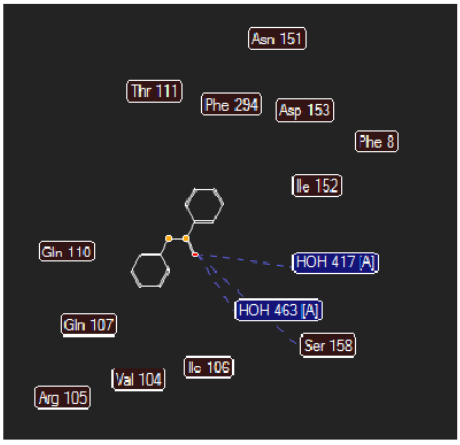
Piperine



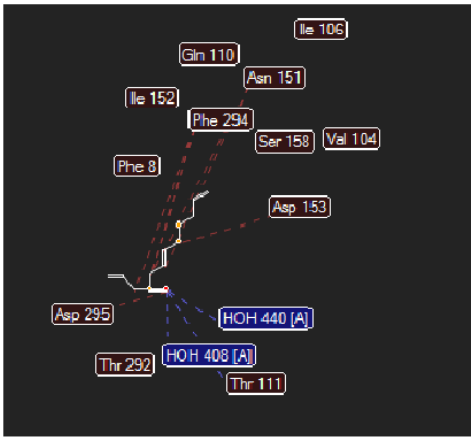
Curcumin



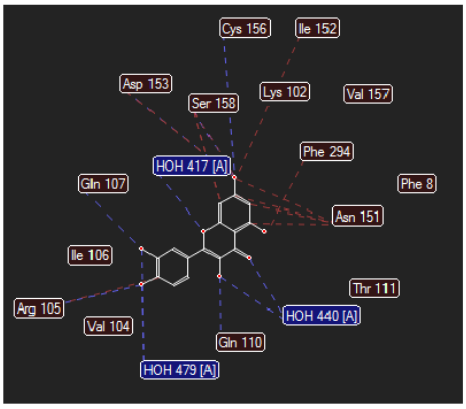
Gingerol



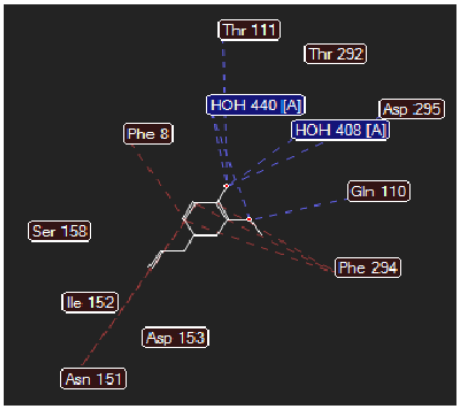
Diphenylthiosulfinate



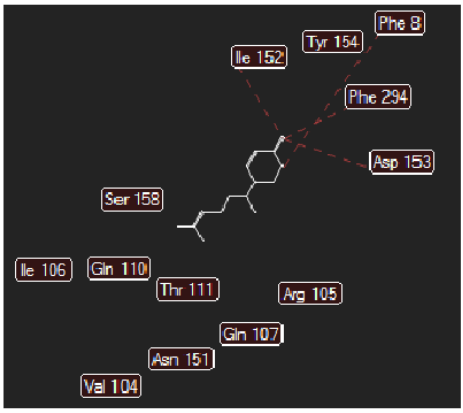
Ajoene



Quercetin

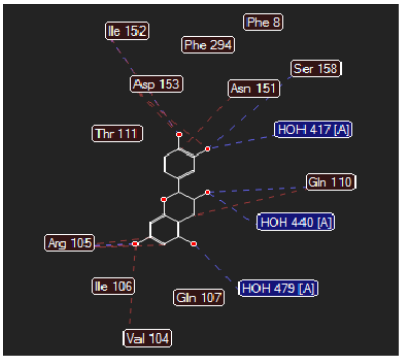


Cinnamaldehyde

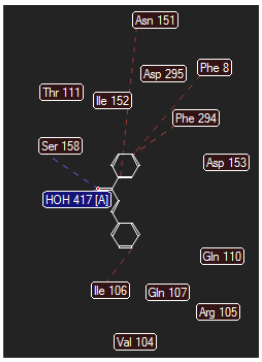


Zingiberene

Figure 2. Steric and hydrogen bond interactions between spices compounds and COVID_19 protease amino acids are put into the active site of the protease virus.



Catechin



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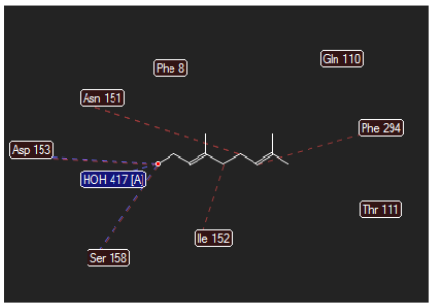
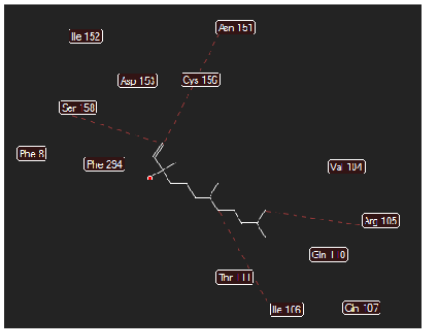
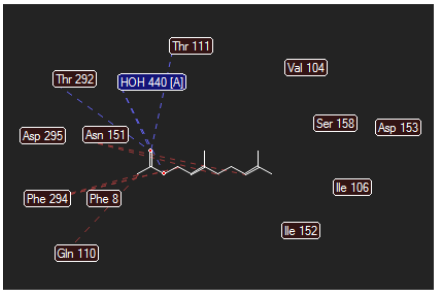


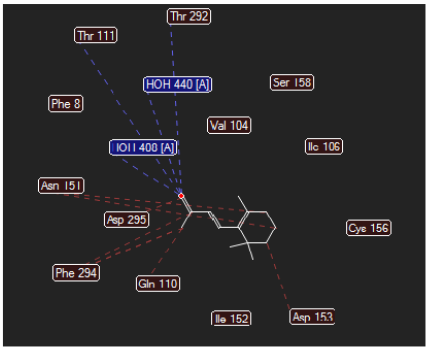
Nerol



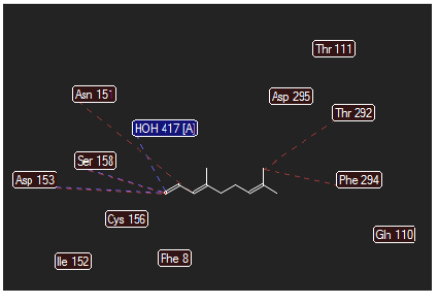
Nerolidol



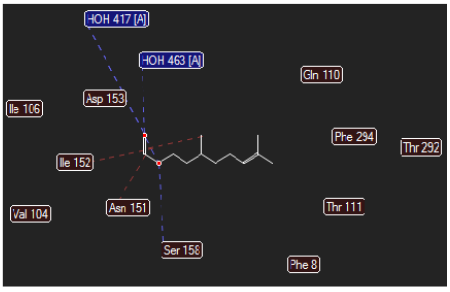
Geranyl Acetate



Beta-Ionone



Citral



Citronellyl Acetat

Figure 3. Steric and hydrogen bond interactions of aromatic compounds with COVID_19 protease, amino acids are put into the active site of the protease virus (2-D interaction diagram).

DISCUSSION

The compounds studied in this study are secondary metabolites of spices that we usually use in our food. The aim of this study was to investigate the inhibitory effect of secondary metabolites on spices and how they bind to coronavirus protein. These spices include turmeric, ginger, cinnamon, cayenne pepper, garlic and onion. In previous studies, their effects on various diseases have been shown. We also added the effect of binding secondary metabolite of tea to this study and we also looked at some aromatic compounds that are present in spices or flowers. Because these compounds are vaporizable enough to be transmitted to the olfactory system and can enter the respiratory tract, they are likely to have a beneficial effect on killing the virus due to the presence of the virus in the lungs. From time immemorial, spices have been an integral part of human nutrition. In different cultures, different spices have been widely used to enhance the color and taste of food. The hot and cold nature of spices has multiplied the uses of spices. Despite scientific advances in medicine and health and industrial advances, we still see an increasing use of spices today. Medicinal properties along with the good taste and smell of this group of edible spices have greatly increased their use. For this purpose, I used spices compounds. Many aromatic compounds are made during natural biochemical reactions, reactions such as fruit growth. These spices include Aromatic compounds, Linear Terpenes, Cyclic Terpenes, and Esters. The largest group of compounds in essential oils and plant fragrances are related to esters. The use of esters is generally low risk. Properties associated with esters include: antifungal, anti-inflammatory, antispasmodic, sedative effects [8,9]. Various studies have been conducted on the effects of these compounds, some of which are mentioned here. Including antimicrobial activity of cinamaldehide [10,11], anti-inflammatory of cinamaldehide, cytotoxicity, anti-oxidative and anti-inflammatory activity of chalcones, Antimicrobial and antiviral effects of nerol, citral, citronellol, geraniol, geranyl ester, Antiviral activity of nerolidol [12,13,14,15], antiviral of Ionone. Effect on cough and antiviral ginger, cytotoxicity and antiviral activity against herpes simplex virus type 1 (HSV-1) were evaluated for the

pepper, It has been demonstrated that curcumin as a plant derivative has a wide range of antiviral activity against different viruses, Natural piperine as a new alternative against influenza viruses [16,17,18,19], Antiviral effect of catechins in green tea on influenza virus. Therapeutic effects of various forms of Garlic such as: Tablets, capsules, essential oils, etc. against herpes viruses 2 and 1 types, influenza A and B, cytomegalovirus, rhinovirus (Vesicular stomatitis virus), pneumonia viruses, coronavirus and HIV have been studied. The antiviral activity of these plants appears to depend on the compounds allicin, ajoene and thiocyanates. It should be noted that the higher the level of these compounds, the higher their antiviral activity. Quercetion sulfur compounds, which are mostly of the flavonoid type of onion, in addition to having antiviral activity, are also used to increase the antiviral power of drugs [20,21,22]. A similar example of this study has been done in another study. capsaisin, piperine, gingerol, cinamaldehyde, nerolidol, geranyl acetate and citral were repeated in both studies. The difference between the two studies is in the use of different software. In the previous study, the autodock software was used, but in this study we used MVD software. Both software do almost the same thing, but how to calculate the connection energy in software is different [23]. The compounds studied in this research had strong binding affinities with one enzymatic flap and formed the strongest bonds with the amino acids asparagine151, aspartate153 and phenylalanine294. By interacting with the active site of the enzyme, these compounds can inhibit these amino acids during the catalytic process. Secondary metabolites are used as medicines, perfumes, spices and essential oils. Therefore, due to the intense interaction of these natural compounds with the protected areas of the coronavirus protease enzyme and its inhibition, these compounds can be considered as effective antiviral drugs and may have the least side effects. Spices and herbs have been used as medicines for centuries, but they cannot be used for complete cure and 100 % of diseases because many of the results on the effects of herbs are laboratory and definitive research has not yet been proven. In addition, excessive consumption of aromatic herbs and spices can damage the digestive system, especially the stomach. In any case, the benefits of spices can be used.

CONCLUSION

Based on the results of the present study, it could be concluded that the compounds

investigated can interact with important amino acids in the enzyme flap to inhibit activity the new coronavirus protease enzyme and inhibit the virus replication. Therefore, these spices could be prescribed as a complementary treatment for patients with coronavirus infection in their food, but this study requires clinical investigation.

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