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Molecular Docking Study of Novel COVID-19 Protease with Low-Risk Terpenoids Compounds of Plants

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Abstract

Background: Due to the reported high ability of virulence of COVID-19 in recent months, several studies have been conducted to discover and introduce COVID-19 antiviral drugs. The results of numerous studies have shown that protease inhibitors and compounds, which make up the major part of plant derivatives, especially terpenoids, can therefore be very effective in controlling virus-induced infection. The aim of this research is the bioinformatical study of COVID-19 inhibition by terpenoids of plant origin.

Materials and methods: This is a descriptive-analytic study. In the present study, the structure of Terpene compounds were received from the databases such as PubChem and COVID-19 proteases were received Protein Data Bank (PDB). After that, molecular docking was performed by MVD (molegro virtual docker) software.

Results: The results are identified to have inhibitory activities against novel COVID-19 protease. Of these compounds, Ginkgolide A has a stronger bond and high affinity with protease. The amount of connecting energy from high to less in order Ginkgolide A>DiThymoquinone>Noscapine>Salvinorin A>Forscolin>Bilobalid e>Citral>Beta Selinene>Menthol. All of these compounds were linked to the intermediate flap that the software had predicted, and all of them were binded to 8 residues, and a total of 19 residues were binded.

Conclusion: Finally, with due attention to the high effectiveness function of terpenoids, we can conclude that these compounds may be considered as effective COVID-19 antiprotease drugs. Also, due to the formation of blood clots in coronavirus infection, a number of these compounds, in addition to antiviral activity, have an effect on inhibiting coagulation.

Keywords: COVID-19 • Coronavirus • Bioinformatic • Terpenoid • Docking

Introduction

On 7 January 2020, a new coronavirus, 2019-nCoV (now officially named SARS-CoV-2) was implicated in an alarming outbreak of a pneumonia-like illness COVID-19, originating from Wuhan City, Hubei, China. Human-to-human transmission was first confirmed in Guangdong, China [1]. The World Health Organization has declared this a global public health emergency on 23 May 2020, there are more than 5 M confirmed cases reported, and the death toll is over 300,000. In the height of the crisis, this virus is spreading at a rate and scale far worse than previous coronavirus epidemics. Coronaviruses contain a genome composed of a long RNA strand one of the largest of all RNA viruses. This genome acts just like a messenger RNA when it infects a cell, and directs the synthesis of two long polyproteins that include the machinery that the virus needs to replicate new viruses. These proteins include a replication/transcription complex that makes more RNA, several structural proteins that construct new virions, and two proteases. The proteases play essential roles in cutting the polyproteins into all of these functional pieces. It is a dimer of two identical subunits that together form two active sites. The protein fold is similar to serine proteases like trypsin, but a cysteine amino acid and a nearby histidine perform the protein-cutting reaction and an extra domain stabilizes the dimer. This structure has a peptide-like inhibitor bound in the active site [2,3].

Bioinformatics is one of the most important and innovative approaches in the design and manufacture of new drugs. Due to the high cost of clinical and laboratory trials, the time consuming and the possibility of error, various bioinformatics techniques are nowadays used in the design of new drugs. Molecular docking, simulation, target point determination and chemical stability studies are the most important bioinformatics methods used in drug design. In the meantime, molecular docking of a special place in the process of designing new drugs, examining and comparing their efficacy Enjoyable [4,5]. Docking was carried out by MVD software in this study. Differential evolution was introduced by Storn and Price [6]. The docking scoring function of MVD is based on PLP originally introduced by Gehlhaar, et al. [7] and latter modified by Yang in 2004 and is extended with a new term, taking hydrogen bond directionality into account. Moreover, a re-ranking procedure is applied to the highest ranked poses to further increase docking accuracy. PDB file often have poor or missing assignment of explicit hydrogens, and the PDB file format cannot accommodate bond order information [8].

One of the novel therapeutic strategies for virus infection apart from the design and chemical synthesis of protease inhibitors is the search for inhibitors of this enzyme among natural compounds in order to obtain drugs with minimal side effects. Among these, Terpenoids are of particular importance due to their high diversity and low IC50 and presence in plant and microorganisms. Terpenoids are the major secondary plant constituents, with more than 36,000 species reported so far [9]. Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, and by some insects. They often have a strong odor and may protect the plants that produce them by deterring herbivores and by

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attracting predators and parasites of herbivores. Although sometimes used interchangeably with "terpenes", terpenoids (or isoprenoids) are modified terpenes as they contain additional functional groups, usually oxygen-containing. The name "Terpene" is derived from the word "Terpentine", an obsolete spelling of the word "Turpentine". Terpenes are also major biosynthetic building blocks. Steroids, for example, are derivatives of the triterpene squalene. Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers. Essential oils are used widely as fragrances in perfumery and traditional medicine, such as aromatherapy. Synthetic variations and derivatives of natural terpenes and terpenoids also greatly expand the variety of aromas used in perfumery and flavors used in food additives [9-12]. These compounds have numerous medicinal properties including Anti-cancer [13], Anti-oxidant [14], Anti-inflammatory, antiviral [15], and antibacterial [16].

Methods

This research was a descriptive-analytical study. In this study, the interaction of Terpenic compounds as described in Figure 1 was investigated. In order to obtain the 2 and 3 dimensional structure of the compounds, a PubChem database (https://pubchem.ncbi.nlm.nih.gov) was used. The PDB database (https://www.rcsb.org/) was used to obtain the complete structure of the protease enzyme. The structure mentioned in access number 6lu7 was received in the PDB database [17].

No.	Compound Name	Source	2D Structure
1	Dithymoquinone	*Nigella sativa*	
2	Salvinorin A	*Salvia divinorum*	
3	Bilobalide	*Ginkgo biloba*	
4	Citral	*Backhousia citriodora*	
5	Menthol	*Mentha*	
6	Ginkgolide A	*Ginkgo biloba*	
7	Noscapine	*Papaveraceae family*	
8	Forskolin	*Plectranthus barbatus*	
9	Beta Selinene	*Apium graveolens, Artemisia annua L, Leonurus sibiricus*	

Figure 1. Name and structure of the Terpenoids studied.

Molecular docking

MVD automatically detects potential binding sites (cavities) using the cavity detection algorithm. To mechanize benchmarking, cavities within a 30 × 30 × 30 Å3 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 (Figure 2). For each ligand docking, the best orientation for the ligand-protein complex was analyzed and hydrogen bonds were identified and labelled. 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). In this study, molecular docking MVD software (https://omictools.com) was used to investigate the molecular interaction between Terpene compounds and protease enzyme. This software enables three-dimensional observation of the interaction between Terpene and protease enzyme virus of the amino acids participating in the interaction between the functional and functional groups on the Terpene molecules (Figure 3). In the present study, all docking conditions for Terpene compounds, the number of interactions, the interaction area, the protease enzyme and the rate of docking were considered to minimize error. In this study, molecular docking between Terpenoids and protease with the ability to investigate the interaction between hydrogen-electrostatic and van der Waals reactions in the active site of the enzyme was performed and the results were compared.

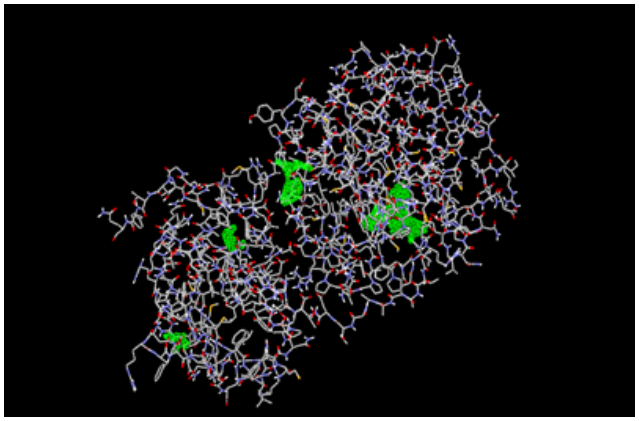

Figure 2. Four cavities that are expected to be drug-binding in these protezae.

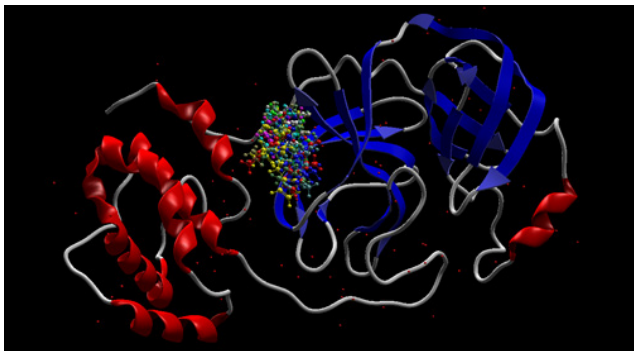

Figure 3. Interactions between the terpene compounds and COVID_19 proteases are put into the active site of the protease virus.

Results

The results of this study indicate the strong interactions of Terpenoids in the two enzymatically protected flap regions. Connecting to the above mentioned areas is highly desirable. The results for the binding of these compounds are summarized in Tables 1-3. 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. By binding these drugs to the active site of the enzyme, the protease cannot be converted to its active state, which is a dimer. All of the studied compounds have been linked to 8 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 Phenylalanine 294. According to the results in the Table 1, these compounds are connected to 19 residues, of which all compounds are connected to 8 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. In Salvinorin A, the amount of binding energy to Asn151 is -16, Asn156 is -15, Phe294 is -22. In Bilobalide, the amount of binding energy to Asn151 is -17, Asn156 is -8.1, Phe294 is -21. In Citral, the amount of binding energy to Asn151 is -12, Asn156 is -12, Phe294 is -15. In Menthol, the amount of binding energy to Asn151 is -17, Asn156 is -14, Phe294 is -6.9. In Ginkgolide A, the amount of binding energy to Asn151 is -16, Asn156 is -11, Phe294 is -8.9. In Noscapine, the amount of binding energy to Asn151 is -11, Asn156 is -5.6, Phe294 is -19. In Forscolin, the amount of binding energy to Asn151 is -19, Asn156 is -14, Phe294 is -16. In Beta Selinene, the amount of binding energy to Asn151 is -15, Asn156 is -13, Phe294 is -17 (Figure 4). However, 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, or moldock score, as shown in Figure 1.

Discussion

Recently, doctors have found that in severe cases of Covid-19, patients develop blood clots [18]. Therefore, Terpenes that have both antiviral effects and prevent blood clots can be effective. Therefore, in this study, we examined 9 Terpenes that have previously been shown to have antiviral or anticoagulant effects. So far, none of the drugs in this study have been clinically tested on coronavirus or in silico, but similar studies have been done with other synthetic drugs, some of which are mentioned here. Several antiviral medications: Zanamivir, Indinavir, Saquinavir, and Remdesivir show potential as and 3CLPRO main proteinase inhibitors and as a treatment for COVID-19 [19]. In another study, the docking of ten plant molecules was studied, among them Oxyacanthine and Hypericin have shown good binding efficacy among others [20]. In one study, researchers studied the binding of proteins to the main virus with eight drugs belonging to four classes of drugs: antimalarial, antibacterial, antiseptic and antihistamine. Among the eight compounds studied, Lymecycline and Mizolastine were identified as possible inhibitors of coronavirus protease [21]. In another study, 318 phytochemicals performed by docking studies showed better inhibitory action on protease are Piperolactam, Quercetin, glucoside, Schaftoside, Chrysoeriol, Isosakuranetin, neohesperidoside, Delphinidin, Petunidin, Riboflavin, Oleanolic acid, caffeoylquinic, Absinthin,

Table 1. The sum of the energies resulting from the interaction of terpenoids and protease enzymes.

No	Compound name	Total energy	Ester bond	Hydrogrn bond	SElectrostatic bond
1	DiThymoquinone	-97	-100	-7	0
2	Salvinorin A	-85	-101	-6	0
3	Bilobalide	-81	-83	-5	0
4	Citral	-67	-60	-1.4	0
5	Menthol	-54	-54	-2.4	0
6	Ginkgolide A	-113	-118	-3	0
7	Noscapine	-98	-94	-6	0
8	Forscolin	-85	-98	-5	0
9	Beta Selinene	-63	-64	0	0

Table 2. The amount of binding energy of protease amino acids to terpenoids.

AA	Arg	Asn	Asp	Asp	Cys	Cys	Gln	Gln	Ile	Ile	Lys	Phe	Phe	Phe	Pro	Ser	Thr	Thr	Val
	105	151	153	295	156	160	107	110	106	152	102	8	112	294	293	158	111	292	104
		-16	-11.6			-7.4	-7.6	-13.3	-5.2		-1.7		-11.5		-3.3	-1	9	9	9
AA	Arg	Asn	Asp	Asp	Cys	Cys	Gln	Gln	Ile	Ile	Lys	Phe	Phe	Phe	Pro	Ser	Thr	Thr	Val
	105	151	153	295	156	160	107	110	106	152	102	8	112	294	293	158	111	292	104
		-16	-11.6			-7.4	-7.6	-13.3	-5.2		-1.7		-11.5		-3.3	-1	9	9	9
AA	Arg	Asn	Asp	Asp	Cys	Cys	Gln	Gln	Ile	Ile	Lys	Phe	Phe	Phe	Pro	Ser	Thr	Thr	Val
	105	151	153	295	156	160	107	110	106	152	102	8	112	294	293	158	111	292	104
		-16	-11.6			-7.4	-7.6	-13.3	-5.2		-1.7		-11.5		-3.3	-1	9	9	9
AA	Arg	Asn	Asp	Asp	Cys	Cys	Gln	Gln	Ile	Ile	Lys	Phe	Phe	Phe	Pro	Ser	Thr	Thr	Val
	105	151	153	295	156	160	107	110	106	152	102	8	112	294	293	158	111	292	104
		-16	-11.6			-7.4	-7.6	-13.3	-5.2		-1.7		-11.5		-3.3	-1	9	9	9

Table 3. The amount of energy of hydrogen bind in compounds with water.

	HOH 408	HOH 417	HOH 440	HOH 456	HOH 463	HOH 479
Residue ID	7	16	39	55	62	78
DiThymoquinone		-6.9	-7.9		2	0.9
Salvinorin A	-2.5	-2.4	6.8	-0.78	-0.4	-2
Bilobalide	-1.6	-1.5	7	-0.4	-5	
Citral	3.2	-0.9	1.7		-0.4	
Menthol		-1.5		-1.7	-11.6	
Ginkgolide A		-7.2	-7.3		-3.8	-0.7
Noscapine	-0.5	-2.9	-0.5	2.8	-3	-0.7
Forscolin	-1.2	-3.9	-2.7	-0.5	-4.5	-1.2
Beta Selinene		-1.9	-1.6	-1.1	-1.6	

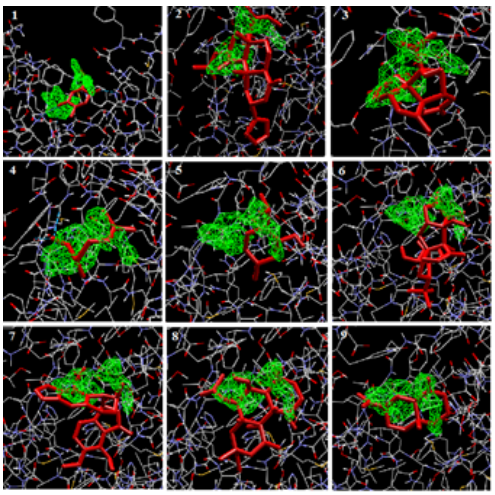

Figure 4. The interaction between terpene compounds in the active site of the protease enzyme virus. 1: Dithymoquinone, 2: Salvinorin A, 3: Bilobalide, 4: Citral, 5: Menthol, 6: Ginkgolide A, 7: Noscapine, 8: Forscolin, 9: Beta Selinene.

Anabsinthin, Dicaffeoylquinic acids [22]. Preliminary results from a study show that Indinavir and Remdesivir have the best docking scores, and a comparison of where the two drugs shows a near perfect dock in the overlap region of the protein pocket [23]. According to previous studies, as well as research on coronavirus infection, drugs have been selected based on coronavirus protease or the virus itself. However, given that coronavirus infection causes blood clots and eventually a stroke, medications that can help prevent clots can also be effective. In this study, we used the recently released crystal structure of COVID-19 proteinase and low-risk or safe herbal medicines for docking analysis. The results of this study showed that the Terpenoids studied can effectively inhibit the COVID-19 proteinase. Terpenes have therapeutic properties ranging all the way from anti-bacterial to anti-inflammatory and more. Turns out, there are also many Terpenes with virus-fighting properties. Salvinurine is one of the active ingredients of Salvia divinorum that has been proven to have analgesic and anti-inflammatory properties in previous studies [24]. Ginkgo biloba is rich in flavonoids and terpenoids. In Chinese medicine, this plant has been used because of its beneficial effects on stimulating general blood circulation and its dilating effects, especially in people with asthma. It is also due to its effects on blood coagulation; Is used. in one study examined the influence of Ginkgo biloba leaf extract (EGb) on the infectivity of influenza viruses in Madin-Darby canine kidney (MDCK) cells. These results suggest that EGb contains an anti-influenza A and B virus substances that directly affects influenza virus particles and disrupts the function of hemagglutinin in adsorption to host cells [25]. In one study was to compare the antiviral activities in vitro of citral, limonene and essential oils (EOs) from Lippia citriodora and L. alba on the replication of yellow fever virus (YFV). Citral and EOs were active before and after virus adsorption on cells [26]. In a study, the effect of menthol on Coxsackievirus B was investigated and showed antiviral effects [27]. The most medicinal properties of this plant are related to Thymoquinone [28]. Anti-inflammatory, antioxidant, immune-boosting effects have led to the release of several pharmacological effects of black seed [29]. Noscapine, a medication used for the treatment of cough, has been shown to inhibit bradykinin enhanced cough response in man. Since it has already been marketed as a cough medicine in a number of countries, it is possible to determine the appropriate dose for the new coronavirus [30]. Forskolin has long been used in traditional medicine to treat asthma and various ailments. In one study, the effect of Forskolin on asthma patients was shown to improve lung function after treatment [31]. In another study, the essential oils obtained from the medicinal plant root Leonurus sibiricus were used. The essential oils of this plant include beta-selinene. The anti-inflammatory and antimicrobial activity of this plant was investigated and reduced inflammatory factors [32]. These compounds can effectively inhibit residues of protease during the catalytic process by interacting with the key amino acids active site. The software identified five protected areas of the enzymatic flap. The Terpenoids studied in this research had strong binding affinities with middle enzymatic flaps and formed the strongest bonds with the amino acids Asparagine 151, Aspartate 153 and Phenylalanine 294. These three amino acids are in the highly conserved and catalytic region of the enzyme (Figure 5). So, low-risk drugs can be designed to bind to these three amino acids. Therefore, due to the strong interaction of natural Terpene compounds with enzymatically conserved regions and specific functional ability, these compounds can be introduced as effective anti-drugs due to their natural origin and less likely to cause side effects if the interactions are enhanced. During chemical processes and microbial biodegradations can be suitable substitutes for synthetic drugs. People are also more likely to take herbal remedies because they have fewer side effects; so it is best to focus on these drugs to treat new coronavirus infections, but it requires clinical studies.

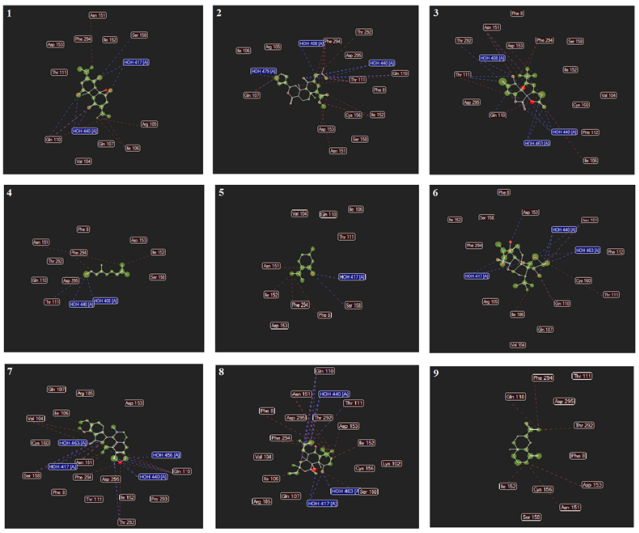

Figure 5. Steric and Hydrogen Bond Interactions between Terpens and COVID_19 proteases Amino Asids are put into the active site of the protease virus: 1: Dithymoquinone, 2: Salvinorin A, 3: Bilobalide, 4: Citral, 5: Menthol, 6: Ginkgolide A, 7: Noscapine, 8: Forscolin, 9: Beta Selinene.

Conclusion

Based on the results of the present study, it can be concluded that the investigated Terpenoids can interfere with the important amino acids in the enzymatic cavity to inhibit the protease enzyme virus. Nine neutral drugs and low risk, namely, Dithymoquinone, Salvinorin A, Bilobalide, Citral, Menthol, Ginkgolide A, Noscapine, Forscolin, Beta Selinene are identified to have inhibitory activities against novel COVID-19 protease. Of these compounds, Ginkgolide A has a stronger bond and high affinity with protease.

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