

DOCKING STUDY ON SOME COMPOUNDS FROM *NIGELLA SATIVA* FIXED OIL AS STERILIZING AND INHIBITING AGENTS AGAINST NOVEL SARS-COV2

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Abstract: Since 31 December 2019, COVID-19 has put the world in a difficult situation among its rapid spreading, rise the deaths, and lack the specific treatment. Under the difficult situation in Iraq, we try to introduce this study by molecular docking to recognize possible inhibitors of COVID - 19 from the fixed oil *Nigella sativa*. This plant has incredible curative properties and is used as a natural remedy against an assortment of ailments. Spike protein and Main protease from coronavirus were chosen as a target for six selected compounds in *Nigella sativa* fixed oil represents saturated and unsaturated fatty acid, docking of these compounds into the active site of spike protein (PDB 7BZ5) gives an energy complex almost (-6.66710901 Kcal /mol) for stearic acid which is better than other sterilizing agents (Ethanol -3.00467157 Kcal /mol and Isopropyl alcohol -3.22151923 Kcal /mol) and that gives us an idea for using *Nigella sativa* fixed oil as a sterilizing agent. Docking into the Main protease (PDB 7BUY) active site demonstrated that linoleic acid provides approximately (-7.24567175 Kcal /mol) energy score and that is better than the given energy score by using nafamostat (-5.90499163 Kcal /mol). Stearic acid plus linoleic acid appeared to have the best effect on COVID-19 virus and we need more clinical experiment to evaluate the medicinal uses of these compounds and we hope this article open prospects to use this plant for COVID-19 treatment.

Keywords: Covid-19, *Nigella sativa*, Fixed oil, Spike protein, Main protease, Linoleic acid, Stearic acid

INTRODUCTION :

COVID-19 is abbreviated for Coronavirus disease 2019, which makes happen by SARS-COV2, which was isolated from respiratory samples collected from patients in Wuhan the China's city, after spreading of this disease in Dec. 2019. Its arrival to Iraq and the first case confirmed in Najaf by April 2020. The number of confirmed cases reached over 964,435 spreading in all provinces of Iraq at the time writing this article. Coronaviruses are a big family of viruses that can cause illness in humans as well as animals. Nearly 7 of these viruses can produce people's infection all over the world but there is 4 coronaviruses commonly infected human: HKU1, OC43, NL 63, and 229E. These are regularly cause respiratory system infects, the with different ranges starting

in the common cold to more hard symptoms diseases like(SARS)Severe Acute Respiratory Syndrome, and(MERS)Middle East Respiratory Syndrome and lately revealed Coronavirus (COVID -19) causes infectious disease ^[1], in history (MERS) and (SARS) have a considerably greater case of rates of fatality than COVID -19. Until now COVID -19 is more infectious, the new SARS-COV2 virus spread very easily among people leading to a larger number of cases. Despite the lesser rate of fatality, the number of total death from COVID -19 is much more than that of MERS and SARS. The rate of transmission for SARS-CoV2 is upper than SRAS- CoV and the cause may possibly be genetic recombination happening in the region of RBD at S protein of SARS-CoV2 which may have heightened the viral transmission capacity ^[2]. S (spike glycoprotein) is a type I transmembrane protein that is made of a big ectodomain, a single pass anchor of transmembrane, and a short intracellular C-terminal tail. The starring role of the S-protein is important for cell adherence and access to the host cell ^[3]. Sneezing and coughing without putting a cover on the mouth can diffuse the virus everywhere, shaking or touching hands with a person who carries or is infected by the virus can pass the virus to another individual. Coronaviruses can infect a large number of people at any time during their lifespan, mutation occurs effectively by coronaviruses, which made them so infectious and spreadable ^[4]. The highest important strategy for preventing viral spread includes: Wash hands with and water soap continuously. If there is no soap, use at least 60% alcohol containing disinfectant. Avoiding touch the facial components with hands. disinfecting and Cleaning repetitively surfaces that can touched ^[5]. Due to a potential shortage of hand sanitizers in stores, and also the repeated use of alcoholic gel to sterile hands causes skin dryness that makes scientists look for alternatives sterilizers by using plant sources. In traditional folk medication, *N. sativa* Seeds have been used for the treatment of different purposes in ancient medical systems of Arabic, Chinese, and Unani for a very extended period, about 28 to 36% of *Nigella sativa* seed contains a fixed oil and mainly composed of many compounds such as unsaturated fatty acids that are linolenic, linoleic, eicosadienoic and arachidonic and the other fatty acids(saturated ones) which include myristicin, palmitic and stearic ^[6]. In the present investigation we studied the effect of six compounds in *Nigella sativa* seed fixed oil against Spike protein S1 [7BZ5] and Main protease [7BUY] in COVID-19 virus to develop a new hand sterilizer solution instead of alcohol gel, The study was done by (MOE) the Molecular Operating Environment software to identify a natural product as a sterile agent.

Material and methods :

Medicinal herb

Black seeds (Heba Sawada) it's a famous shrub in the east and has numerous health applications. Black seed fixed oil has been used in traditional medicine due to much

therapeutic medicine in this research we choose six compounds in *Nigella sativa* fixed oil linoleic, myristic, linolenic acid, stearic, oleic, and palmitic acids^[6-7].



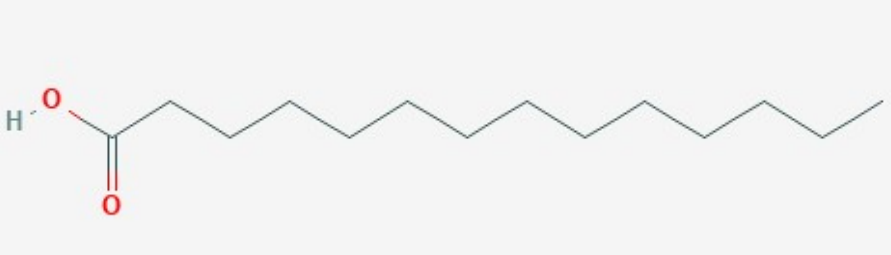
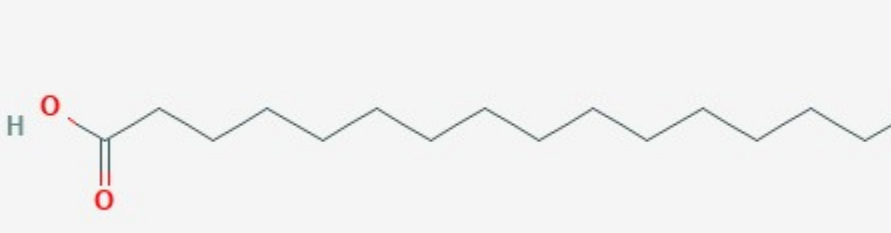
Preparation of both proteins and ligands

Three-dimensional structures of Spike protein S1 and Main protease Covid-19 were downloaded from Protein Data Bank under PDB ID 7BZ5 and 7BUY respectively^[8-9]. The 7BZ5 and 7BUY Crystallographic properties were illustrated in Table (1. and 2), which shows six *N. sativa* L chemical compounds that were selected in this research from the literature^[6-7]. The three dimensional structures of *N. sativa*'s selected compounds were downloaded from PubChem <https://pubchem.ncbi.nlm.nih.gov/>. in .sdf format, also the physicochemical parameters rules of Lipinski for each ligand were calculated and illustrated in Table (3). Chemical structures of sterilizing agents and drugs under clinical tests for treatment of COVID-19 are reported in Table(4 & 5). By Molecular Operating Environment software (MOE), the receptor's preferred region that can interacts with ligands is acknowledged as (active site prediction) were identified and the protocol of isolation by means of field strengths in the Amber10 (Assisted Model Building With Energy Refinement) energy of the protein was minimized. That followed by removing of H₂O molecules from the surface of protein therefore during docking the interaction region will be clear and not hidden. The active sites of 7BZ5 and 7BUY were recognized by using the MOE's site-finder module as revealed in Figures (1 & 2) respectively. Moreover, under default circumstances of pH = 7 and temperature = 300°K both natural ligands (compounds from *N. sativa*), sterilizing agents and proposed drugs were submitted to energy minimize.

Table (1): The S1protein and Main protease Crystallographic properties

Protein and enzyme	Code of PDB	Classification	system of Expression	Resolution	Identification Method	Total structure weight (kDa)	chain
COVID - 19 S1 protein	7BZ5	protein immune system of Virus	Spodoptera frugiperda, Homo sapiens	1.84 Å	X-RAY DIFFRACTION	73.36	A
COVID - 19 Main protease	7BUY	Protein of Virus	<i>Escherichia coli</i> BI21 (DE3)	1.60 Å	X-RAY DIFFRACTION	34.36	A

Table (2): The chemical structures of selected *N. Sativa* fixed oil's compounds

Name of compounds	Chemical structures
Linoleic acid	
Linolenic acid	
Myristic acid	
Palmitic acid	


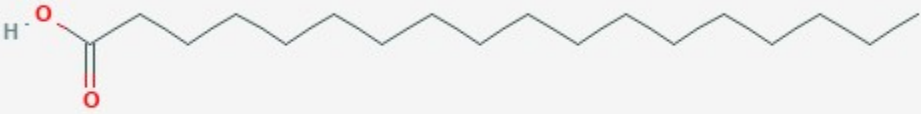
Oleic acid	
Stearic acid	

Table (3): physicochemical parameter of Lipinski's roles for selected *N. sativa* fixed oil's compounds

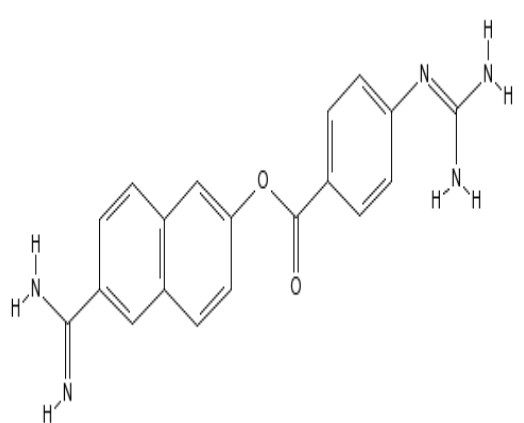
Compounds	Mol. Weight g/mol	h_log P	h_log S	a_acc	a_don	TPSA (Å ²)	b_rotN	lip_druglike
Linoleic acid	280.45	6.59	-6.59	2	2	37.29	14	1
Linolenic acid	278.43	6.07	-6.22	2	2	37.29	13	1
Myristic acid	228.37	5.58	-5.26	2	2	37.29	12	1
Palmitic acid	256.42	6.60	-6.30	2	2	37.29	14	1
Oleic acid	282.46	7.10	-6.96	2	2	37.29	15	1
Stearic acid	284.48	7.62	-7.34	2	2	37.29	16	1

Table (4):The chemical structures of the sterilizing agents used against COVID-19

Sterilizing agent	Chemical structure
Ethanol	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{H}-\text{C}-\text{C}-\text{O}-\text{H} \\ \quad \\ \text{H} \quad \text{H} \end{array}$

Isopropyl alcohol	$ \begin{array}{ccccc} & \text{H} & & \text{H} & & \text{H} \\ & & & & & \\ \text{H} & - \text{C} & - & \text{C} & - & \text{C} & - \text{H} \\ & & & & & \\ & \text{H} & & \text{OH} & & \text{H} \end{array} $
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Table (5): The chemical structure for COVID-19 treatment proposed drug.

Drug	Chemical structure	CID of Pub Chem	Properties of Lipinski	
			Properties	Value
Nafamostat		4413	MW g/mol	349.39
			LogP	-2.31
			LogS	-1.19
			H-donor	0
			H-acceptor	1
			TPSA (Å ²)	143.91
			b_rotN	5
			lip_druglike	1

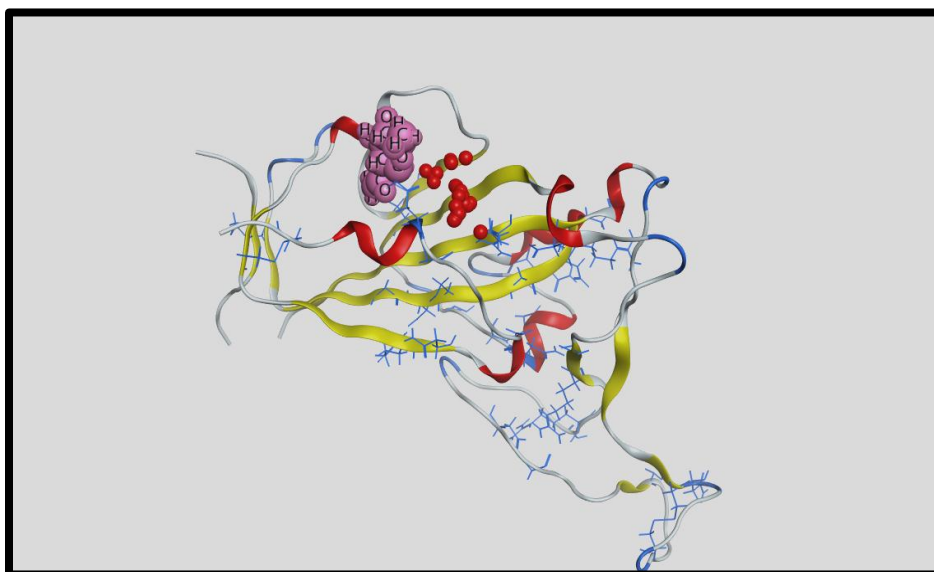


Figure (1): The 7BZ5 isolated active site in complex with 2-acetamido-2-deoxy-beta-D-glucopyranose inhibitor

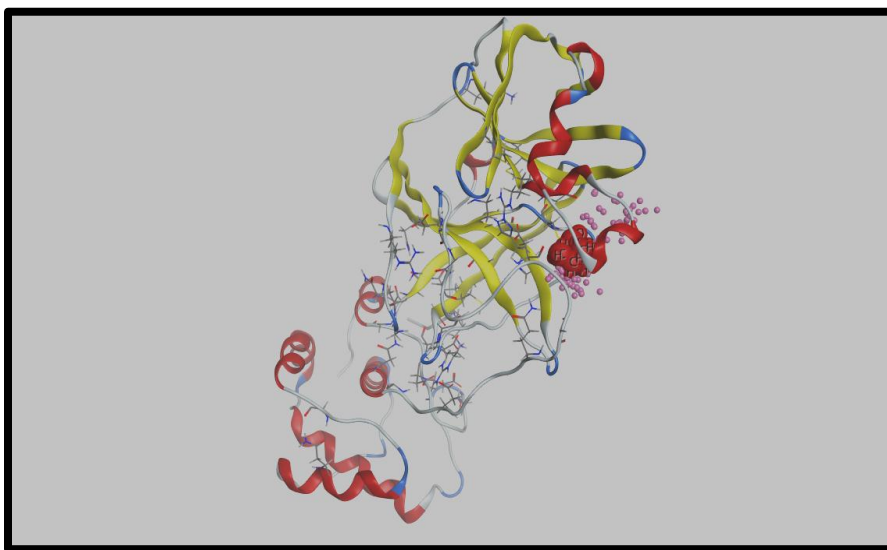


Figure (2): The 7BUY isolated active site in complex with hexylcarbamic acid inhibitor

Molecular docking studies :

Molecular docking of six compounds in *Nigella Sativa* fixed oil was performed to predict its binding with 7BZ5 and 7BUY, by using MOE software tools. The docked conformation of the compounds with the lowest free energy with most of the default tools to predict in what way (ligand or molecules) interact with the receptor's binding site. In the 1st docking process we use the six compounds from *Nigella sativa* fixed oil with 7BZ5 in comparison with Ethanol and Isopropyl alcohol to evaluate the ability to use the compounds in *Nigella sativa* fixed oil for sterilization. The second docked process was performed between the same *Nigella sativa* fixed oil compounds with 7BUY in comparison with the Nafamostat drug ^[10-11]. Table 6 illustrate obtained scores

from Ethanol and Isopropyl alcohol with 7BZ5 in comparison with obtained scores of selected compounds in *Nigella sativa* fixed oil with the same protein while Table 7 shows docking scores for Nafamostat drug with 7BUY in comparison with docking scores of selected compounds in *Nigella sativa* fixed oil with the same enzyme.

Table 6: Obtained docking score by selected compounds from *N. sativa* fixed oil with 7BZ5

Selected compounds from <i>Nigella sativa</i> fixed oil	Score (Kcal /mol) 7BZ5
Linoleic acid	-6.360425
Linolenic acid	-6.10005331
Myristic acid	-5.42579079
Palmitic acid	-6.12277222
Oleic acid	-6.17033482
Stearic acid	-6.66710901
Compounds used as sterilizing agents	Score (Kcal /mol) 7BZ5
Ethanol	-3.00467157
Isopropyl alcohol	-3.22151923

Table 7: Obtained docking score by selected compounds *N. sativa* fixed oil with 7BUY

Selected compounds from <i>Nigella sativa</i> fixed oil	Score (Kcal /mol) 7BUY
Linoleic acid	-7.40788746
Linolenic acid	-7.01706076
Myristic acid	-6.50507784
Palmitic acid	-6.63255215
Oleic acid	-7.24567175
Stearic acid	-6.56722403
Drug	Score (Kcal /mol) 7BUY
Nafamostat	-5.90499163

Results :

Obtained results showed all the selected compounds in *Nigella sativa* fixed oil give the best score compared to other sterilizing agents (Ethanol, Isopropyl alcohol) in complex with S1protein 7BZ5. Stearic acid gave the highest score (-6.66710901 Kcal /mol) with 7BZ5 (Figure 3A,3B), while the best score with the Main protease 7BUY gave by linoleic acid (-7.24567175 Kcal /mol) (Figure 4A,4B) in comparison with Nafamostat.

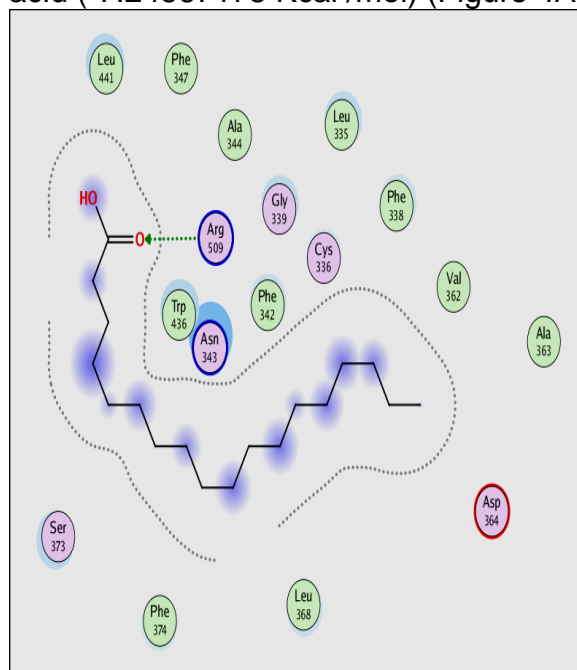


Figure (3A): The two dimensional diagram of interaction for stearic acid with 7BZ5 2D

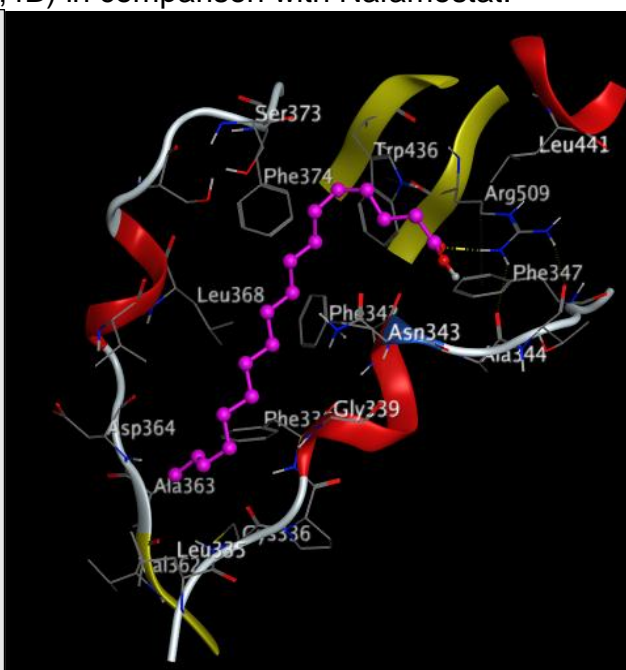


Figure (3B): The three dimensional diagram of interaction for stearic acid with 7BZ5

Stearic acid in complex with 7BZ5 shows one hydrogen possible interaction(H-acceptor) with ARG509 amino acid with a distance of 2.85 Å and energy of -2.8 Kcal / mol. Interactions of the rest compounds from *N. sativa* fixed oil with 7BZ5 were illustrated in Table(8). While Table 9 illustrates the interaction between the rest compounds and 7BUY.

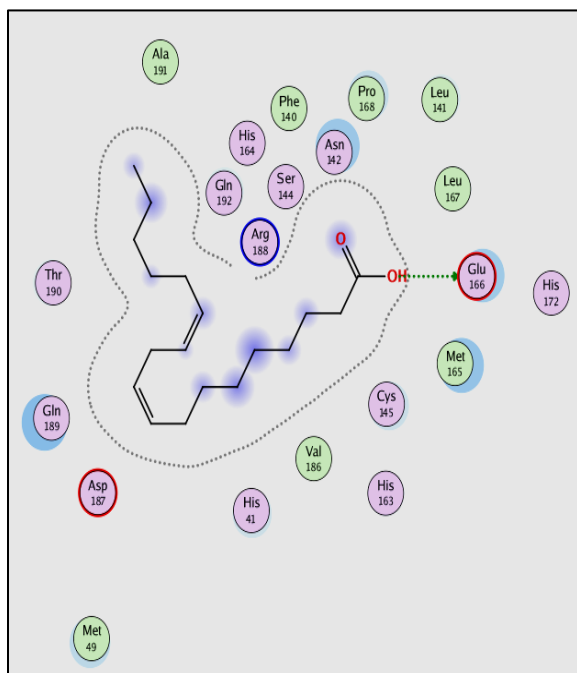
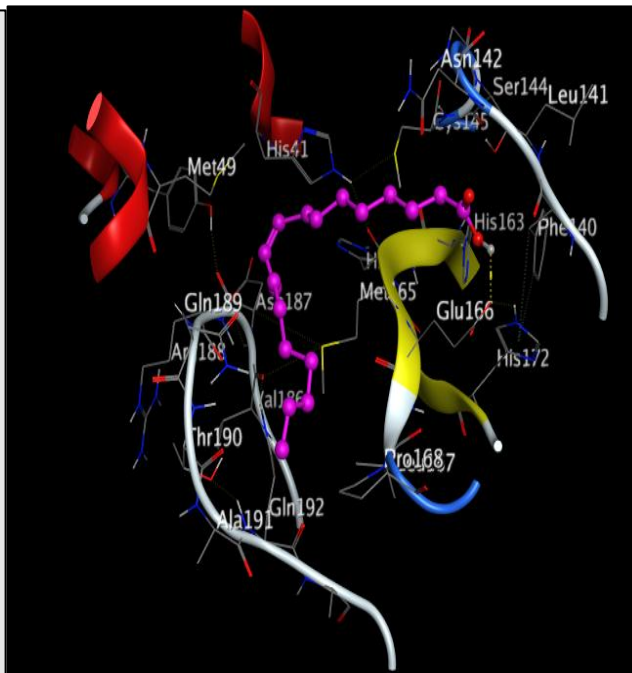


Figure (4A): The two dimensional diagram of interaction for linoleic acid with 7BUY

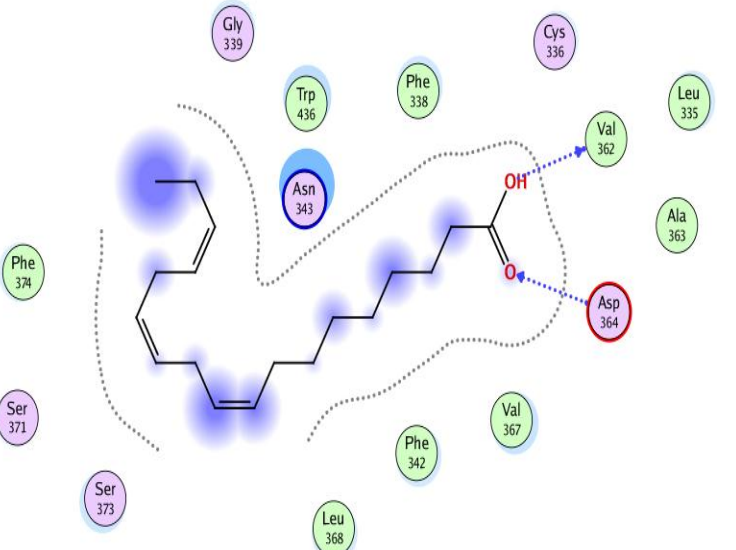


Figure(4A): The three dimensional diagram of interaction for linoleic acid with 7BUY

Table (8): The 2dimensional diagrams for interactions of the selected *N. Sativa* fixed oil's compounds with 7BZ5

Selected compounds from <i>Nigella sativa</i> fixed oil	2D diagrams for structure interaction	Type of interaction
Linoleic acid		<p>One hydrogen reaction is possible with:</p> <ul style="list-style-type: none"> - VAL362 amino acid (H-donor) with 3.21Å distance & - 2.1 Kcal / mol energy.
Selected compounds from <i>Nigella sativa</i> fixed oil	2D diagrams for structure interaction	Type of interaction

Myristic acid		<p>One hydrogen reaction is possible with:</p> <ul style="list-style-type: none"> - TRP436 amino acid(H-acceptor) with 2.97\AA distance & -1.9 Kcal / mol energy.
Palmitic acid		<p>Three possible hydrogen reaction with:</p> <ul style="list-style-type: none"> - GLY339 amino acid (H-acceptor) with 3.19\AA distance & -1.0 Kcal /mol energy - ASN343 amino acid (H-acceptor) with 2.16\AA distance & energy of -6.9 Kcal /mol - ASP364 amino acid (H-acceptor) with 3.26\AA distance & -1.9 Kcal /mol energy.

Selected compounds from <i>Nigella sativa</i> fixed oil	2D diagrams for structure interaction	Type of interaction
Linolenic acid		<p>Two possible hydrogen bonds with:</p> <ul style="list-style-type: none"> - VAL362 amino acid (H-donor) with 3.17Å distance & -1.2 Kcal/mol energy, ASP364 amino acid (H-acceptor) with 3.31 Å distance & -1.1 Kcal/mol energy.

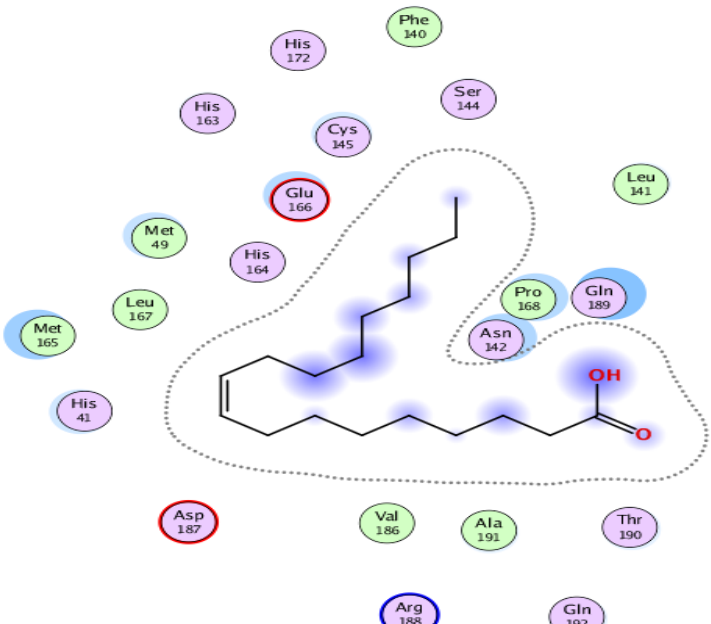
Oleic acid		There is no noticeable interactions, only electrostatics -Van der Waals - interactions.
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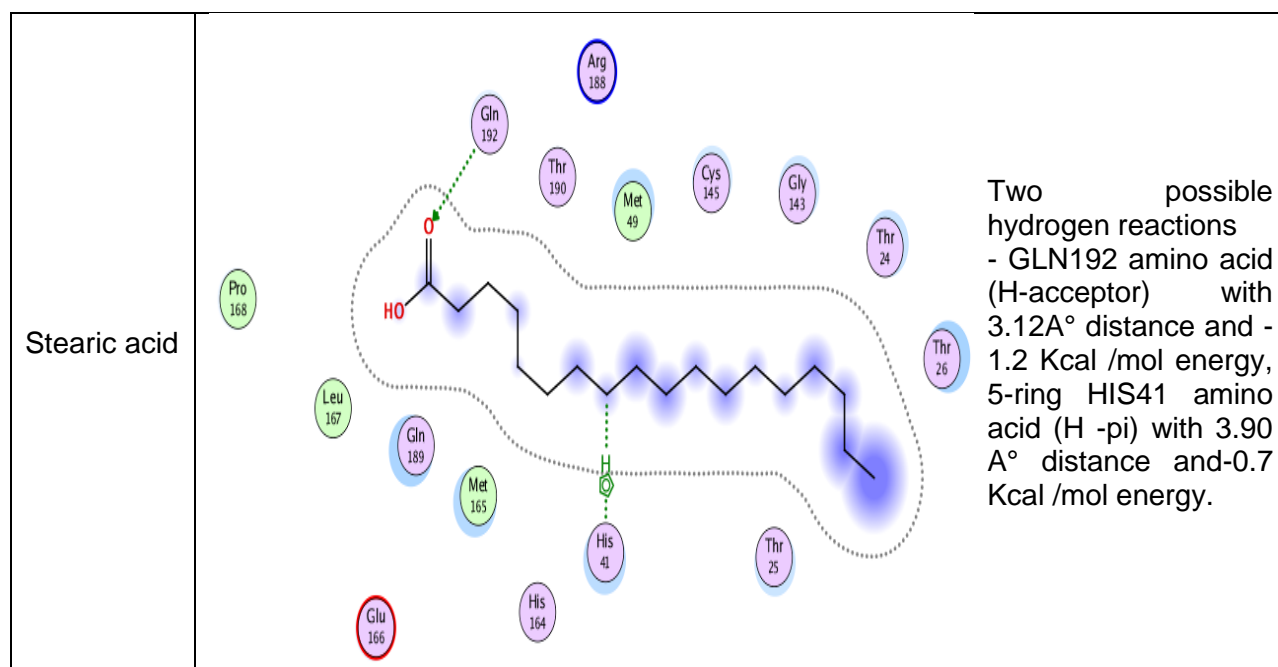
Table (9): The 2dimentional diagrams of interactions for selected *N. Sativa* fixed oil's compounds with 7BUY

Selected compounds from <i>Nigella sativa</i> fixed oil	2D diagrams for structure interaction	Type of interaction
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Myristic acid		<p>Two possible hydrogen reaction :</p> <ul style="list-style-type: none"> - THR190 amino acid (H-acceptor) with 3.61\AA distance & - 0.6 Kcal / mol energy, GLN192 amino acid (H-acceptor) with 3.37\AA distance & - 0.6 Kcal /mol energy.
Palmitic acid		<p>Two possible hydrogen bonds with:</p> <ul style="list-style-type: none"> - GLN189 amino acid (H-acceptor) with 3.02\AA distance & - 1.5 Kcal / mol energy, 5-ring HIS41 amino acid (H -pi) with 3.88\AA distance & -0.7 Kcal /mol energy.
Selected compounds from <i>Nigella sativa</i> fixed	2D diagrams for structure interaction	Type of interaction

oil		
Linolenic acid		<p>Two possible hydrogen bonds:</p> <ul style="list-style-type: none"> - THR190 amino acid (H-acceptor) with 3.29Å distance & -2.8 Kcal/mol energy. - GLN192 amino acid (H-acceptor) with 3.27 Å distance & -0.8 Kcal/mol energy.

Oleic acid		There is no-noticeable interactions, only electrostatics-der Van Waals-interactions.
Selected compounds from <i>Nigella sativa</i> fixed oil	2D diagrams for structure interaction	Type of interaction



Discussion :

Humanity today faces a great challenge against a dangerous disease which is called COVID-19, this disease is caused by the genus betacoronavirus. The invisible virus-like SARS-CoV-2 has been affected by the human population as well as countries and world economy, climate, and global environment. The problem is until nowadays there is no product of effective drugs against the pandemic SARS- CoV2 and many vaccines that targeting different SARS-CoV2 proteins is still in progress ^[12]. The first step to discover a drug for COVID-19 treatment is begun by study the virus structure (genome and proteins), SARS- CoV2 is an enveloped, positive sense, single- RNA strand. The expression of Gene fragments can give structural and nonstructural proteins, like [(spike)S, (envelope)E, (membrane)M, and (nucleocapsid)N] proteins genes that encode structural proteins, while the ORF region is coded for the non-structural ones, for instance papain like-protease, RNA-dependent RNAPolymerase, and 3-chymotrypsin like- protease ^[13-14]. In this article, we discuss two important proteins (S protein and Main protease). The spike glycoprotein candidate as a target for COVID-19 drug, this protein responsible for the initial binding of previous SARS-CoV1 coronaviruses to the host cells receptor Angiotensin Converting Enzyme 2 (ACE2), the protein of ACE2 can expressed in many human body organs mostly in the intestine, lungs, and kidney and considered as the main targets of the SARS-CoV2 that mediating viral cell entry and the spike protein activation by proteolytic cleavage. Also the crown appearance under electron microscopy may be related to the glycoprotein of spike (or

“spike protein”) that studs all the surface around the coronavirus ^[15-13]. Thus, prevent the binding to ACE2, or blocking cleavage of S glycoprotein by host protease and reject the release of the fusion peptide is an effective way to prevent the entrance of coronavirus ^[16]. The other protein in this study is the enzyme Main proteinase(Mpro), the viral infection depends on the processing of viral's polyprotein, an event catalyzed by the (Mpro) (which is renowned as 3CLpro too). Later main proteinase is found only in virus and not in the host cells that made this protein a noticeable target for production of antiviral medicine against SARS- CoV2 infections ^[17]. To develop drugs that help peoples around the world who are infected by coronavirus we return to nature and choose fixed oil in *Nigella sativa* seeds, which is, a Ranunculaceae family member that is publicly famous as (black seed). or seeds of *N. Sativa* with a wealthy religious and historical experience is the marvel remedial plant for the whole illnesses, excepting death. The seeds of *N. Sativa* are broadly used for getting the significant fixed oil ^[18]. The seeds contain between 28 to 36% of fixed oil and are chiefly composed of unsaturated fatty acids that are (linolenic, arachidonic, oleic, linoleic, and eicosadienoic)acids, as well as saturated fatty acids which include (myristicin, palmitic, and stearic)acids ^[6]. The result from the docking study indicates that stearic acid gives the lowest score of energy (-6.66710901 Kcal /mol) in complex with 7BZ5 also the other selected compounds gives high score such as linoleic acid (-6.360425 Kcal /mol) (Figure 3A,3B) and (Table 8) when compared with other docked compounds (Ethanol and Isopropyl alcohol) which are used for sterilizing because this compounds have the ability to disrupt the structure of the cell, and coagulating and/or denaturing the microorganisms proteins ^[19]. In contrast, the best score of selected compounds from *Nigella sativa* fixed oil may be indicated to the ability of these compounds to destroyed the spike(S- protein) in the COVID -19 virus, previous study described that the antiviral activity of human milk is due to the presence of fatty acid, the study also indicates that fatty acid such as linoleic acid can be caused leakage of vesicular stomatitis virus (VSV) envelopes ^[20]. Previous studies also demonstrate that fatty acid extracted from the skin, hair, and nail exhibit antimicrobial agents, a little known about the mechanism of the activity of fatty acids and of some revisions proposed that the mechanism includes pores formation in the bacterial cell membrane and/or bacterial cells lysis, which indicates a possible distraction of numerous processes in cells either by the interfering of a spatial organization or by binding directly with proteins, The research also established that antimicrobial action is meaning of carbon chain length in addition to the presence, orientation, as well as double bonds' number, leading to the suggestion that fatty acids have complicated mechanisms and could contain different mechanisms for altered combinations of bacteria and lipid ^[21]. From these clarifications, the *Nigella sativa* fixed oil could be a good choice as a sterilizing agent against coronavirus. The results also showed that the lowest score of energy provides by linoleic acid (-7.24567175 Kcal / mol) also the other selected compounds gives a good score such as

oleic acid (-7.24567175 Kcal / mol) (Figure 4A,4B) and (Table 9) in complex with 7BUY in comparison with other docked compound (Nafamostat) which is a serine protease synthetic inhibitor permitted in Japan for anticoagulation in extracorporeal circulation treatment as well as acute pancreatitis disseminated intravascular coagulation, today this drug used for COVID-19 patient because it's thought inhibits SARS-CoV2 cell entrance^[22]. Per contra linoleic acid, oleic acid, and other selected compounds give a better score than Nafamostat, the previous study in 2009 showed that there is an antiviral activity for the lipophilic extract and fatty acids of many edible plant against *Para-influenza-3* virus (PI-3) and *Herpes simplex* virus type-1 (HSV-1) as compared to oseltamivir and acyclovir, the extracts of this plant were found to be rich in saturated and unsaturated fatty acids such as (myristic, linolenic palmitic, , oleic, and linoleic) acids the study demonstrated that the hexane extracts had a strong activity against both viruses, which lead us to think that the antiviral activity almost attributed to the action of this nonpolar compounds^[23]. Another study also about the fatty acids' antiviral activity as well as their soap against the influenza virus, illustrated that viral suspension that prepared from the infected mices' lungs, was mixed at room temperature and pH 7.5 with a soap solution or fatty acid. The infectivity for the samples were tested in mice by intranasal inoculation, the first time after 90 minutes and again after 24 hours,. The earliest experiments revealed that linoleic acids and oleic deactivated the virus^[24]. From this result, we can conclude its possible to use fatty acids from a natural source as a source to design a new drug to help the people infected by coronavirus especially when we know that fatty acids are existing in plant and animal species and play important roles in the metabolic processes and structure of cell membranes^[25].

Conclusion :

The existent study aims to distinguish natural sources molecules that can inhibit SARS - CoV2 by working on (the Spike and Main protease) proteins. The result from molecular docking illustrated that stearic acid and linoleic acid from *N. sativa* fixed oil can inhibit the COVID -19 virus and give a better score than other agents used against this virus. These results gave hope to utilize the fixed oil from *Nigella sativa* as a traditional remedy against the virus.

Acknowledgment:

We would like to express our heartfelt thanks to departments of Pharmacognosy and medicinal plants, Clinical Laboratory Sciences and human anatomy, in both Pharmacy and medicine Colleges, the University of Basra for their assistant and effort during the study.

Conflict of interest:

There is no conflict of interest.

Authors' Contributions:

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Funding:

None

Data Availability

The datasets analysed during the current study are available in the PDB, and PubChem web site generated by the corresponding author.

Ethics Statement:

This article does not contain any studies with human participants or animals performed by any of the authors.

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