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Quantitative Structure-Activity Relationships and Molecular Docking Simulation of Allicin Compounds as Inhibitors of COVID-19 Protease Enzyme

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ABSTRACT

Background: Coronavirus (CoV) is a group of viruses that cause disease in humans and animals. These viruses contain crown-shaped spike glycoproteins on their surface.

Objective: We conducted a quantitative structure-activity relationship (QSAR) study on a series of 36 compounds of allicin to assess their antiviral activities against the main protease of COVID-19.

Methods: In the present descriptive-analytic study, the information on the structure of compounds, the COVID-19 protease enzyme, and the Allicin derivatives was obtained from the databases such as the Research Collaboratory for Structural Bioinformatics' Protein Data Bank (PDB) and PubChem. The QSAR method, analysis of correlations and multiple linear regressions were carried out. Six molecular descriptors such as constitutional and molecular topology descriptors were selected for the model. Finally, molecular docking was performed in iGEMDOCK 2.1 software.

Results: The obtained multi-parametric model reported a correlation coefficient of about 0.89, indicating that the model was able to satisfactory predict the antiviral activity of allicin compounds.

Conclusion: The findings obtained can be valuable in designing, synthesizing, and developing novel antiviral agents with allicin-based scaffold.

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1. Introduction

One of the challenges of human society is to deal with the diseases that endanger human health. Finding effective drugs to treat these diseases or reduce their complications has been the most important concern [1]. Coronavirus (CoV) is a group of viruses that cause disease in humans and animals. These viruses contain crown-shaped spike glycoproteins on their surface [2]. Coronaviruses are a group of viruses from the family of coronaviridae which includes alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus as well as several subgenera and species. Human coronaviruses (HCoVs) include HCoV-NL63 and HCoV-229E belonging to the alpha coronavirus type, and HCoV-HKU1 and HCoV-OC43 belonging to Embecovirus subgenus of beta coronavirus type. They were later identified as HCoV OC43 and HCoV-229E [3]. The beta coronaviruses include four lineages (subgroups) of A, B, C, and D. The lineage A, as human pathogens, consists of HCoV-HKU1 and Betacoronavirus 1 (HCoV-OC43). The lineages B and C comprise Severe Acute Respiratory Syndrome-related Coronaviruses (SARS-CoV, SARS-CoV-2) and the Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV), both as human pathogens [4].

Numerous studies have shown that garlic possesses antimicrobial properties which can inhibit the growth of different types of organisms *in vitro*, and is widely used as a systemic and topical antimicrobial agent [5]. Allicin in garlic represents 70%-80% of the total thiosulfinates. Typically, alliinase converts alliin to allicin. Allicin, once broken down, produces other products such as diallyl disulfide, diallyl sulfide, and dithiins. Simultaneously, the compound gamma-glutamyl cysteine is converted to S-allylcysteine, through a biochemical pathway other than the alliin–allicin pathway [6].

Recognition of molecular structures is the key point in understanding the performance of molecules, because of the existence of relation between the structure and the properties of a compound which links it's microscopic and macroscopic characteristics to each other. Since the laboratory works in the field of energetic materials are very costly and risky, the methods and models to predict the properties of these materials have been wildly used in recent years. For developing a model with good reliability and high predictive power, there is a need for the selection of proper molecular descriptors. A descriptor is a numerical representation of the chemical information of a molecular structure [7]. Molecular dynamic (MD) simulation, molecular docking, and quantitative structure-activity relationships (QSARs) are valuable computational methods for drug design and activity prediction.

In the MD simulation and molecular docking techniques, the three-dimensional structure of the proteins, including their receptors, are provided and ligand-receptor-interactions has a prominent role; thus, this method involves a structure-based drug design. Molecular docking method suggests the desired energy and orientation of ligand in the protein active site to build a stable complex. The MD simulation is used to study protein-ligand binding. QSAR method can help achieve the favored data and information with the minimum cost and time. QSAR is known as ligand-based drug design because it is performed based on the knowledge about ligands. The QSAR study is a perfect way for understanding the drug design process based on their chemical interaction and pharmacological activity. The QSAR models summarize the relationships between chemical structures and their biological activities independent of the receptor [8]. The QSAR method consists of four types of computationally derived descriptors including electronic, stearic, hydrophobic, and topological indices to correlate with pharmacological activities [9].

The QSAR provides information about the relationship between chemical structures and their biological activity which is important in selecting or removing the compound before synthesis and testing [10]. It is important to predict the results, especially when it is not possible to test a compound experimentally. Molecular descriptors that are the most important elements in obtaining a QSAR model, can be found experimentally or via mathematical computation from various theories such as chemical graph theory, quantum mechanics, and information theories [11]. The present study aims to develop a QSAR model on a series of allicin analogues with respect to their half maximal inhibitory concentration (IC50).

2. Material and Methods

This is a descriptive-analytical study. The QSAR equations were developed to investigate the antiviral biological activity (inhibition of virus protease enzyme) of a set of 6 molecular descriptors (Table 1) in order to achieve a quantitative relationship between antiviral activity and structural descriptors and predict the antiviral activity of allicin. The 3D X-ray crystallographic structure of COVID-19 proteases was retrieved from the Research Collaboratory for Structural

Bioinformatics' Protein Data Bank (PDB) freely available in www.rcsb.org. The datasets of inhibitors from allicin derivatives, as selective and potent inhibitors of COVID-19 protease (6LU7), expressed in IC50 were selected from ChEMBL database [12]. The datasets have been thoroughly curated according to the proposed protocol [13]. Their IC50 values were converted to pIC50 values by using their negative logarithm.

Reducing the number of descriptors

One of the problems in creating QSAR models is the large number of independent variables. In most cases, the number of descriptors is higher than the number of molecules where the use of least squares method causes challenges such as random selection and random correlation. Since some descriptors have constant values while others have correlation with each other, the descriptors with constant or near-constant values (>09% fixed data) were removed and those with a correlation >0.9 were examined. Then, a descriptor showing lower correlation with the independent variables was deleted.

Selection of effective descriptors

The most important part in creating an efficient QSAR model is to select the right molecular descriptors. After calculating various descriptors, a number of suitable descriptors were selected to build the model. This step involves finding the descriptors with useful information so that the predictive power of the model be at an acceptable level. The step-by-step method and genetic algorithms were used to select the most appropriate descriptors. The use of genetic algorithms involves a stochastic search of solutions using genetic operators. Genetic algorithms have been widely used in QSAR modeling and chemometrics [14].

In the current study, the optimization of antiviral activity and descriptor generation for inhibiting the 6LU7 activity were achieved by using the semi-empirical method PM3 in HyperChem v.8.0 software. A total of 30 compounds, as the biological data, was used to generate descriptors. The molecular structures were optimized by the Polak–Ribiere algorithm with a root mean square gradient of 0.01 kcal/Å mol. The outputs, produced by the ChemBio3D Ultra 13, were entered into the Dragon software to calculate four types of descriptors including 0D, 1D, 2D, and 3D. The calculated descriptors of the data processing and model building were employed to generate a 30×6 data matrix where each row represents the molecule numbers and each column shows the number of descriptors. The dataset (30 compounds) was categorized into two calibration and validation subsets. The validation subset included 20% of the total data (equal to 6 descriptors with biological activity). The QSAR study was carried out using the Multivariate Linear Regression (MLR) analysis along with the stepwise regression in Excel software. After optimization, all compounds were docked to protease enzyme using the iGEMDOCK version 2.1 software. To confirm the reliability of the results, some compounds were tested in Swiss Dock software [15, 16].

iGEMDOCK v. 2.1

In the present study, the molecular interaction between the garlic compounds and protease enzyme of COVID-19, was evaluated using the iGEMDOCK (iGeneric Evolutionary Method Docking) v. 2.1 software which is used for virtual screening, molecular docking, post-analysis, and visualization of different ligands developed by Jinn-Moon Yang at National Chiao Tung University, Taiwan. This docking software determines the orientation and conformation of ligand in the active site

Table 1. List of molecular descriptors used in QSAR modeling

Descriptors	Descriptor Groups
Wiener index (w)	Molecular topology
Topological Polar Surface Area (TPSA)	Molecular properties
Molecular Weight (MW)	Constituional
Partition coefficient (clogp)	Molecular networks
Mol Refractivity (CMR)	Molecular networks
Molecular Topological Index (MTI)	Molecular topology

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of the target protein. After docking, the iGEMDOCK generates protein-ligand interaction profiles of Electrostatic (Elec), Hydrogen-bonding (Hbond), and Van der Waals (vdW) interactions. The docked poses were visualized by RasMol. The empirical scoring function of iGEMDOCK is estimated as follows (Equation 1):

1. Fitness=vdW+Hbond+Elec

In our study, to minimize the errors, all docking conditions for herbal compounds and standard drugs including the used software, the number of interactions, the area of interaction, the protease enzyme, and the docking speed were considered to be the same. In the docking method, the number of interactions was 70 and the interaction area was 200 angstroms.

3. Results

Totally, our study had six descriptors for which we considered 30 training data and five test data. In the present study, the nonlinear function p(x)/q(x) was used to calculate the prediction values of training and test observations. Genetic algorithm was used to calculate its coefficients. In this algorithm, the population size was 2000 chromosomes. The roulette wheel was used to select the chromosomes. To measure the mutation rate, the constraint dependent method was used. For crossover, the method was scattered and its rate considered to be 30%. We decided to stop the algorithm after 200 generations, and then the parameters were adjusted to obtain the best value for the fitness function (R^2). According to the algorithm, a R^2 value of 99% is acceptable Equation 2.

2. $y = \frac{a_0+\sum_{i=1}^{6} a_i * descriptor_i}{b_0+\sum_{i=1}^{6} b_i * descriptor_i}$

Based on the above equation, the coefficients were obtained as follows:

a=[-1.687, 4.159, -0.943, -1.996, -0.229, 0.28, 0.425], b=[-2.484, 2.778, -3.964, -3.544, 0.551, 0.533, 0.502]

To ensure the accuracy and reliability of the data, the values of R-squared (R^2), Root Mean Square of Error (RMSE) and mean absolute error (MAE) indices for the training and test data were calculated. As shown in Table 2, the R^2 value was 0.89047 for the training data and 0.86816 for the test data which are acceptable, indicating that about 87% of the prediction values are close to the experimental values and the obtained function can show the effect of descriptors on the output proper. The RMSE value was 0.13607 for the training data and 0.10820 for the test data which are acceptable. The higher number of test data caused the RMSE value to be less than that for the training data. Also, the MAE value was 0.07899 and 0.06360 for the test and training data, respectively which are acceptable. Hence, when there is a 6-fold increase in the observations (i.e., from 5 to 30), there is only a 0.1 increase in the error value. The results provide a strong impetus for further research in the recognition of COVID-19.

We used PDBsum website to analyze the docking results. The results showed that the amino acids alanine 2, valine 3, etc. are present at the binding site of the virus protease enzyme (Figure 1) which was consistent with the results of molecular docking in IGEMDOCK v. 2.1. software (Figure 2).

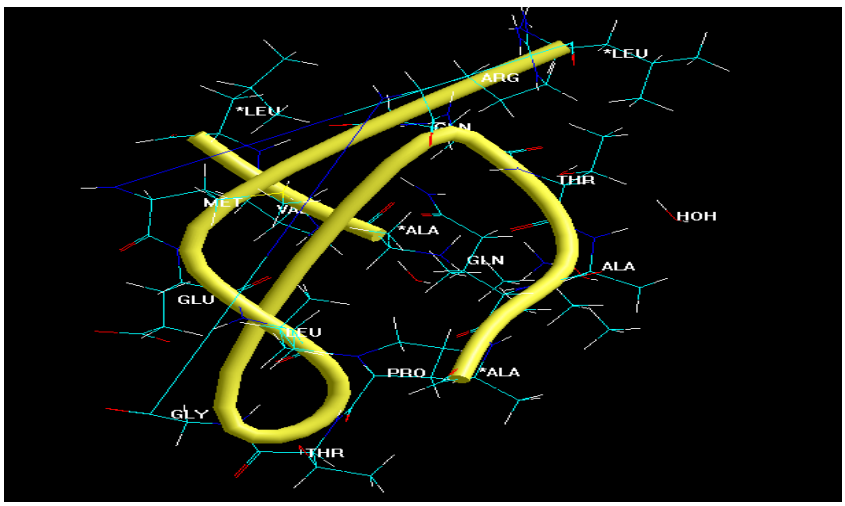

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Figure 1. Interaction and placement of amino acids in the active site of the COVID-19 protease enzyme

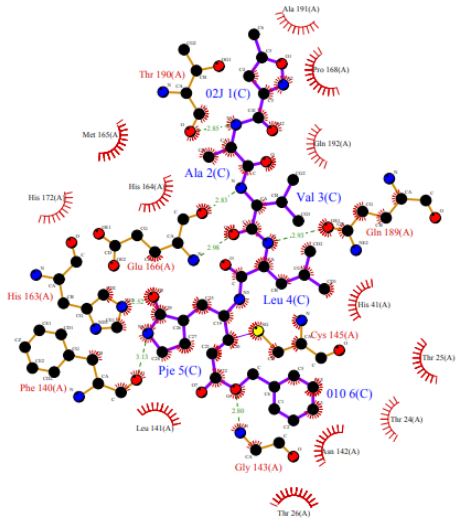

Figure 2. LIGPLOT diagram of interactions involving ligand 02J-ALA-VAL-LEU-PJE-010 extracted from PDBsum website (entry: 6LU7)

4. Discussion

One of the problems that human societies have faced so far is to deal with a variety of diseases that jeopardize their health and have been among the most important concerns of the researchers who are involved in searching for effective drugs. In the past, the process that led to the discovery and development of new drugs was based on a trial-and-error approach, which was both time-consuming and costly. For this reason, the need to use theoretical and computational methods with the potential to predict the properties or activity of drug compounds without testing seems to be inevitable. The advent of chemometrics has opened new horizons to solve these problems [14, 17].

In this research, a QSAR study was performed on allicin compounds as a possible antiviral drug for the COVID-19. Initially, the molecular descriptors were created and the most appropriate ones showing the highest correlation with the drug activity of allicin were selected using the genetic algorithm and appropriate MLR analysis. There was a relationship between the IC50 values of allicin compounds and the inhibitors of COVID-19 protease. The antiviral activity was predicted for allicin. The experimental IC50 values showed an acceptable linear correlation with the predicted IC50 values of allicin-like compounds.

Table 2. Training and test data validation results

Index	Training	Test
$R^2 = 1 - \frac{\sum (Y_{EXP} - Y_{PRED})^2}{\sum (Y_{EXP} - Y_{MEAN})^2}$	0.89047	0.86816
$\mathrm{RMSE} = \sqrt{\frac{\sum (Y_{EXP} - Y_{PRED})^2}{N}}$	0.13607	0.10820
$\mathrm{MAE} = \frac{\sum \lvert Y_{EXP} - Y_{PRED} \rvert}{N}$	0.07899	0.06360

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Table 3. Docking results of the antiviral activity of allicin compounds in the active site of protease enzyme 6lu7

ChEMBL ID	Total Fitness	vdw	HBond	Elec
96	-52.19	-29.3	-23.12	0.24
97034	-52.18	-29.36	-23.06	0.24
289816	-57.88	-48.5	-9.38	0
40439	-74.63	-61.29	-13.34	0
55518	-57.36	-47.38	-9.98	0
53950	-60.63	-47.29	-13.34	0
293258	-72.24	-42.37	-30.37	0
304285	-71.91	-61.05	-10.87	0
79140	-76.8	-54.56	-22.24	0
13310	-53.89	-30.98	-22.91	0
151152	-58.19	-47.42	-10.77	0
351872	-51.03	-46.57	-4.46	0
167373	-46.84	-37.35	-9.49	0
359965	-39.66	-36.16	-3.5	0
207223	-59.78	-52.78	-7	0
207222	-50.49	-31.75	-18.98	0.23
208927	-71.54	-54.44	-26.09	0
2158671	-83.01	-61.5	-21.51	0
2312685	-61.82	-42.57	-20.84	1.59
2312683	-70.09	-51.93	-18.16	0
2312684	-56.88	-37.41	-20.84	1.37
2415009	-50.54	-30.39	-20.39	0.24
2419072	-63.34	-56.34	-7	0
2252189	-45.22	-36.22	-9	0
3116428	-68.29	-56.45	-11.84	0
3218218	-76.63	-53.56	-23.07	0
3291000	-70.48	-54.82	-15.66	0
3291001	-68.07	-52.62	-14.45	0
475341	-77.99	-52.26	-25.73	0
479804	-6994	-47.58	-24.94	2.58
1160593	-69.99	-43.74	-26.25	0
1808516	-78.94	-66.16	-12.78	0
2425817	-75.49	-59.16	-16.33	0
212529	-65.1	-48.77	-16.34	0

ID: Identity; vdw: Van Der Waals Bond; HBond Hydrogen band; Elec: Electrostatic band.

The QSAR study has the ability to quickly generate hundreds of different descriptors. Once the descriptors are calculated, it is necessary to select a number of these descriptors to be included in the QSAR model. Since most of the QSAR equations are linear, the correlation coefficient can provide a proper quantitative method to evaluate how well each descriptor describes the activity. Therefore, the selected descriptors should have the highest correlation coefficient. In the QSAR models, it is assumed that there is a linear or non-linear relationship between the physico-chemical properties and the molecular structure of compounds, indicating that the QSAR tries to establish a set of simple mathematical relationships.

An important limitation of this study was the lack of knowledge about whether the used iGEMDOCK software was able to quantitatively and qualitatively predict the interaction of allicin derivatives with protease enzyme of COVID-19. Generally, in order to validate using a docking method, the crystallographic ligand must be extracted from the active site and be docked again. In this case, the root mean square error of the docked conformity compared to that of initial crystallographic conformity is a measure of the predictability of ligand-binding conformity by docking. According to credible scientific sources, the root mean square error must be ≤2 angstroms to prove the validity of the docking process. Validation of the method was performed using the ligands extracted from the active site of the COVID-19 protease. The predictive accuracy of the binding of substance 2-[(2Bromophenyl) methylsulfanyl]-5-pyrazin-2-yl-1, 3,4-oxadiazole (ChEMBL ID: 2158671) to COVID-19 protease enzyme was more appropriate than that of other compounds of allicin. Hence, the iGEMDOCK software was an acceptable method for predicting how protease binds to allicin compounds (Table 3).

Examination of different compounds of allicin showed that various amino acids such as leucine, proline, valine, and alanine played an important role in establishing key interactions with different compounds. The binding site of the possible COVID-19 antiviral drugs in our study was in agreement with the standard binding site of the crystallographic ligand.

The findings of the present study can help design and propose drug structures with different potencies in binding to the protease enzyme of COVID-19 virus. The result of the study can optimize the pharmacokinetics of possible drugs. Finding of Amgad Albohy showed the structure-based design of natural flavonoids as anti-COVID-19 drugs targeting the nsp10/nsp16 complex [18]. A molecular docking study was performed to analyze the inhibitory function of newly synthetic quinazolinone derivatives against Homo sapiens AKT1 protein. Molecular docking simulations were found to be in accordance with in-vitro studies, and supported the biological activity [19]. It seems that the precise mechanism has not been defined yet. Ghaneian et al. found that garlic extract with a good selectivity index value has inhibitory effects on the virus penetration and proliferation in cell culture [20].

5. Conclusions

The results indicate the ability of QSAR models to predict the antiviral effects of allicin on COVID-19 protease enzyme. The findings obtained can be valuable in designing, synthesizing, and developing novel antiviral agents with allicin-based scaffold. The genetic algorithms are optimal algorithms for selecting the best descriptors for QSAR models.

Ethical Considerations

Compliance with ethical guidelines

The current research was approved by the Ethics Committee of Qazvin University of Medical Sciences (Code: IR.QUMS.REC.1399.367).

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Authors' contributions

Conceptualization and Supervision: Anoosh Eghdami and Hossein Piri; Methodology: Anoosh Eghdami; Investigation, Writing–original draft, and Writing-review & editing: All authors; Data collection: Sayyed Nima Hashemi Ghermezi and Saeede Salemi-Bazargani; Data analysis: Anoosh Eghdami and Sayyed Nima Hashemi Ghermezi; Funding acquisition and Resources: Hossein Piri and Elham Hajialilo.

Conflict of interest

The authors declared no competing interests.

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